On strategic choices faced by large pharmaceutical laboratories and their effect on innovation risk under fuzzy conditions

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Structured abstract

Objectives. We develop a fuzzy evaluation model that provides managers at different responsibility levels in pharmaceutical laboratories with a rich picture of their innovation risk as well as that of competitors. This would help them take better strategic decisions around the management of their present and future portfolio of clinical trials in an uncertain environment. Through three structured fuzzy inference systems (FIS), the model evaluates the overall innovation risk of the laboratories by capturing the financial and pipeline sides of innovation risk.

Methods and Materials. Three FIS, based on the Mamdani model, determine the level of innovation risk of large pharmaceutical laboratories according to the strategic choices they face. Two subsystems measure different aspects of innovation risk while the third one builds on the results of the previous two. In all of them, both the partitions of the variables and the rules of the knowledge base were agreed through an innovative 2-tuple-based method. With the aid of experts, we have embedded knowledge into the FIS and validated the model.

Results. In an empirical application of the proposed methodology, we evaluate a sample of 31 large pharmaceutical laboratories in the period 2008-2013. Depending on the relative weight of the two subsystems in the first layer (capturing the financial and the pipeline sides of innovation risk), we estimate the overall risk. Comparisons across laboratories are made and graphical surfaces are analyzed in order to interpret the results. We have also run regressions to better understand the implications of our results.

Conclusions. The main contribution of this work is the development of an innovative fuzzy evaluation model that is useful for analyzing the innovation risk characteristics of large pharmaceutical laboratories given their strategic choices. The methodology is valid for carrying out a systematic analysis of the potential for developing new drugs over time and in a stable manner while managing the risks involved. We provide all the necessary tools and datasets to facilitate the replication of the system, which may be easily applied to other settings.

Keywords

Fuzzy inference systems; 2-tuple-based method; innovation risk; R&D; Pharmaceutical laboratories

Highlights

- Consensual fuzzy sets and rules are used to model innovation risk in large pharmaceutical laboratories, clarifying the system for pharmaceutical decision-makers and stakeholders.
- With the aid of experts, we have combined knowledge with large and diverse datasets and embedded it into the fuzzy inference systems.
- The fuzzy evaluation model captures both the financial side and the pipeline side of innovation risk of pharmaceutical companies operating in uncertain environments.
- The fuzzy evaluation model we develop in this work has been applied to evaluate innovation risk in a sample of 31 large pharmaceutical laboratories covering the period from 2008 to 2013.

Acronyms

ATC	Anatomical, Therapeutic, Chemical (classification system)
CFO	Chief Financial Officer
CIO	Chief Innovation Officer
CTs	Clinical trials

CTs x Prob	Probabilities of success per ATC from the corresponding phase (I, II, III and IV) of each CT to approval per pharmaceutical laboratory
EMA	European Medicines Agency
FDA	Food and Drug Administration
FIS	Fuzzy Inference System
NCEs	New Chemical Entities
NCEs x Prob	Probabilities of success per ATC from Phase I to Approval of New Chemical Entities
NFTs	Number of financial transactions

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1. Introduction

New clinical trial strategies are being proposed, focused on reducing timelines, optimising clinical development plans, and assessing and managing risks. However, many of those strategies are implemented on an individual trial basis, without considering a fully integrated global development plan. In light of this, a systemic framework for global clinical development analysis and optimization is required (see e.g. Chang et al., 2019).

Given that 70 to 90% of the costs of developing new medicines can be associated with clinical trials (Matsushita et al., 2019), enhancing decision making around the portfolio of critical trials can be expected to result in huge improvements in the healthcare industry. Harrison (2016) studies the reasons for clinical failure based on the reported causes of drug attrition by clinical development. As may be anticipated, the bulk of failures were associated with lack of efficacy (52%) and lack of safety (24%). However, as may not be anticipated, in third place, failures in strategy (15%) appears to be a key factor in clinical trial failure.

Strategic decision making in clinical trials is a hot topic given the need for new and more efficient types of clinical trial designs. The pharmaceutical industry requires de implementation of new strategic approaches to innovative clinical trials design and management of candidate drugs with more potential for success (Janiaud et al. 2019; Verweij et al., 2019). These three examples focus on improving clinical trials targeted at a single disease area (oncology in these three cases). Tucker et al. (2017) propose a new model that integrates information about clinical trials targeted at degenerative diseases such as cancer. They claim that clinical trials are usually conducted over a population within a specific period in order to study certain characteristics of a single health issue or a single disease process. They propose a calibrated model that integrates different sources of incomplete information (cross-section info not

directly related to longitudinal info) in order obtain a better picture in the dynamics of degenerative diseases.

We propose a fuzzy model that captures innovation risk across all the different disease areas to obtain a global picture of innovation risk in a given lab. Prior fuzzy works have shown several applications of fuzzy methodologies in the medical and pharmaceutical industries. Some researchers use this approach to improve medical procedures and training at hospitals, such as Mendez et al. (2018) and Nakawala et al. (2018). From a different prism, Gascón et al. (2007) classify countries depending on their likelihood to consume and produce generics through fuzzy techniques.

Other contributions of fuzzy logic to the healthcare sector focus on strategic decision making at pharmaceutical firms, see e.g. Puente et al. (2011). This prior study takes into consideration that risk issues are key in the pharmaceutical generic industry, often deterring managers from expanding in this business. However, the pipeline management of pharmaceutical companies that only produce generics, without investing in significant R&D, is comparatively simpler. In this article, we develop an innovative fuzzy evaluation model aimed at assessing innovation risk in the pharmaceutical industry. This fuzzy model is designed to help managers at R&D-intensive laboratories take strategic decisions around their portfolio of new drugs. With the aid of experts in Biochemistry, the pharmaceutical industry, and value creation, we have embedded knowledge into and calibrated the FIS and we have validated the operation of the resulting evaluation model.

From this perspective, the contribution of our article is aligned with that by Guo et al. (2018), who construct a model for selecting a portfolio of R&D projects under uncertainty. Their proposal, who takes simultaneously into account strategic issues and financial issues, combines fuzzy techniques with the real options approach. They transform the fuzzy model into a binary linear programming problem, calculating the Pareto frontier than optimizes the proposed multi-objective function. As we do in this work, Guo et al. (2018) consider risk constraints, resource constraints and technological constraints. They apply the model to a single, relatively small, Chinese pharmaceutical company, which is named as “Company X”. Nothing is known about this laboratory, apart from the fact that it was founded in

1994 and started a project scheme in 2002. Every year this company selects a specific number of projects (around 30) to implement from a set of 100 candidate projects.

In our case, we develop an innovative fuzzy evaluation model to analyze innovation risk in a set of large, multinational pharmaceutical companies. In the application of the system we propose, we use only publicly available data from up-to-date datasets of different nature. The fuzzy model combines different information sources to produce the innovation risk outcome, capturing both the financial and pipeline sides of innovation risk that will help managers at R&D intensive pharmaceutical laboratories in their strategic decision-making processes on how to configure their global portfolio of clinical trials. In this sense, the system enables managers to compare the innovation risk of their laboratories with that of competitors, allowing them to visualize simultaneously different perspectives of innovation risk.

The appendices offer more information on the public information datasets that we have used, while the online appendix provides the relevant files associated with our proposed fuzzy model. In light of this, our results can be replicated with our public information datasets or, alternatively, the fuzzy model can be easily applied to investigate innovation risk at different laboratories with alternative datasets.

1.1. Alternative R&D strategies

Large, R&D-intensive pharmaceutical companies are in the business of permanent innovation. Ideally, they should have a stable pipeline of new drugs over time that receives sufficient approvals, year after year, from agencies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), in order to create value for as many stakeholders as possible. If large pharma labs find a way to enhance strategic decisions when configuring the global portfolio of clinical trials, this is going to be good news not only for patients and shareholders but also for regulators and other parties interested in a better functioning of the drug discovery process and eventually for the whole healthcare sector. To this end, adequate financing of the drug discovery process through internal R&D expenditure and financial transactions is fundamental. Thus, it is of utmost importance to balance strategic issues and financial considerations when designing the composition of a R&D portfolio (Carlsson et al., 2007; Lo Nigro et al., 2016; Guo et al., 2018).

Exploring a sample of 37 pharmaceutical laboratories, Gascón et al. (2017) find that most of the large companies in this industry are either fully efficient or close to the efficient frontier. Having said that, there is room to push the frontier forward by taking better-informed strategic decisions about how to configure the portfolio of clinical trials. Assessing correctly the innovation risk level of alternative clinical trial strategic decisions is very relevant to the decision making process.

At this point, it should be highlighted that there are several alternative paths for achieving valuable and sustainable innovation. Some innovators at the frontier have a preference for creating knowledge inside the organization while others to look outside in order to push innovation (Lowman et al., 2012; Macher and Boerner 2012; Schuhmacher et al., 2013; Honig and Hirsch, 2016; Schuhmacher et al., 2016; Trusheim et al., 2016; Gascón et al., 2017). Whatever organizational alternatives are selected, there will be innovation risks that need to be quantified and managed.

Different strategic choices and attitudes toward risk, interplaying with those of competitors of different sizes and R&D characteristics, will yield different outcomes. In this paper, we are mostly concerned with the strategic choices made by large pharmaceutical firms aimed at managing innovation risk in uncertain environments. In such a context, fuzzy methodologies can make a difference. Interestingly, fuzzy applications have been previously proposed for supporting decision-making processes when managers are faced with complex, uncertain, and risky environments, and the dataset is relatively small but with a high number of attributes; see e.g. Li et al. (2011) and Guo et al. (2018). In our case of large pharmaceutical laboratories, there are also many attributes; however, the dataset is extremely large and we need to integrate these large and diverse data sources. In this sense, a team of experts have played a crucial role in the development of the FIS. Finally, we highlight that all the datasets that we employ in this work are publicly available.

1.2. Modelling innovation risk

Several aspects make it difficult to evaluate, in a simple manner, the innovation risk inherent in a given pharmaceutical firm. In this paper, we develop a fuzzy evaluation model for assessing the global innovation risk associated with the portfolio of clinical trials at pharmaceutical companies that is built on four factors that our experts consider crucial to an adequate assessment of innovation risk : (1) R&D

expenditure (R&D); (2) Number of announced Financial Transactions (NFTs); (3) Probabilities of success related to authorized New Chemical Entities (NCEs x Prob); and (4) Probabilities of success of yet-to-be-approved drugs, approximated through Clinical Trials (CTs x Prob). All the sources of data that we used for the construction of inputs are described in Table A.1 (Appendix A).

Under these circumstances, three FIS are designed to integrate all these information sources with the aim of supporting decision-making processes at large pharmaceutical firms. Fuzzy inference systems adequately emulate human reasoning in decision-making processes based on rules from ill-defined or vague data (Lin, 2010) —as has already been proved in many other ambits (Puente et al., 2002; Gascón et al., 2007; García et al., 2013). This approach is therefore perfectly applicable for managing the pipeline of innovative drugs in large pharmaceutical laboratories.

We consider the four factors and we make use of the expert knowledge embedded into the risk assessment model through the knowledge base defined for the FIS —expressed by a set of If-Then rules—, we are able to quantify the innovation risk associated with a large pharmaceutical laboratory from two perspectives: those of the Chief Financial Officer (CFO) and the Chief Innovation Officer (CIO). In addition, and in order to avoid potential biases in the definition of the evaluation system structure, we suggest a new method based on 2-tuples. This is aimed at achieving an agreement between experts on the definition of the partitions of their variables and their rule bases.

All in all, the proposed methodology allows us to manage the high uncertainty inherent in the definition of the knowledge bases needed to develop the evaluation model and facilitates understanding of the evaluation process, constructing a conceptual framework similar to what an expert in the pharmaceutical laboratory sector would have in mind.

1.3. Paper structure

The rest of the paper is structured as follows. In Section 2, the variables used in the evaluation model are described, as are the sources from which these variables come. In Section 3, the methodology proposed for the design of the model is described. This methodology will permit the evaluation of the innovation risk of large pharmaceutical laboratories. Section 4 describes how the methodology is applied

to the particular cases of 31 large pharmaceutical firms. In this section, we also discuss the results obtained. Lastly, in Section 5, we present our conclusions and reflect on some avenues for future work.

2. Data sources, variables and risk evaluation model

To capture the innovation risk of companies in the pharmaceutical industry, we have accounted for the present challenges of drug discovery. Advances in science and technology allow pharmaceutical laboratories to use more varied ways of organizing their acquisition of knowledge in order to foster innovation. The strategic choices taken by laboratories that condition innovation risk are numerous and inter-related. Therefore, we need to choose the most relevant variables to obtain a decision-making model that helps them determine the desired level of innovation risk. We have embedded this compound of knowledge into the FIS with the aid of a team of experts. First, an expert in the biochemical characteristics of authorized new chemical entities and clinical trials. Second, an expert in the pharmaceutical sector, whose laboratory is not part of our sample. Third, a group of experts in the economic and financial variables of value creation at pharmaceutical laboratories.

Each of the four inputs (factors) of our fuzzy innovation risk model, i.e., (1) R&D; (2) NFTs; (3) NCEs x Prob; and (4) CTs x Prob, has its own data requirements. We describe in detail, in Appendix A, the different datasets used in setting up the model. We also explain our choice based on our experts knowledge as well as on previous research articles and literature reviews. Some of these variables have previously been employed in Gascón et al. (2017); in particular, those variables related with the first FIS of the model. Others are specific to the risk evaluation model that we develop in this paper; those related to the second FIS of the model. Our final sample comprises 31 large pharmaceutical firms. In Table A.1 (Appendix A), we have summarized all the problems encountered while merging different sources of data, as well as the solution given to these problems, in order to construct the four inputs of the fuzzy model.

2.1. Input variable 1 – R&D: Pharmaceutical laboratory internal R&D capability

Pharmaceutical laboratories are technology-based organizations that may improve their innovation performance by means of: (1) prior experience in a particular therapeutic area (or disease) that we will

classify according to ATC codes; and (2) diverse overall experience (ATC code diversity). Laboratories with more diverse experience have access to a greater range of knowledge (which can be transferred to a new therapeutic area) than organizations with a more homogenous knowledge base. The greater their R&D capabilities, the more their successful and unsuccessful prior experiences in a particular therapeutic area and the more diverse their overall experience in different therapeutic areas (Granstrand, 1998; Breschi et al. 2003; Almeida and Phene, 2004; Suzuki and Kodama, 2004; Macher and Boerner, 2006; Macher and Boerner, 2012; Boh et al., 2014; Garzon-Vico et al., 2016).

Size per se is not a guarantee of lower innovation risk, and large organizations may be less innovative than smaller ones. However, competition will eliminate inefficient organizations, both large and small, from the market. Even among large pharmaceutical laboratories, some are larger than others. Larger laboratories are able to diversify more and invest in promising drugs in more varied therapeutic areas or diseases. Thus, we expect large efficient pharmaceutical laboratories to organize their R&D activities in an efficient manner as in Gascón et al. (2017). Large laboratories with a greater internal R&D capability have the potential to organize their R&D resources in more varied ways and to draw from experience. Ceteris paribus, we expect laboratories with a greater internal R&D capability to control better and reduce relative innovation risk.

2.2. Input variable 2 – Number of Financial Transactions (NFTs): External R&D

Competitive financial markets allocate funds to the organizations with the greatest potential for implementing new processes and technologies. Thus, laboratories that are active in financial transactions and understand which R&D investments are fundamental key will be more successful in bringing innovative drugs to the market with lower innovation risk. The way innovation is financed shapes the type of R&D that is undertaken (Haleblian and Finkelstein, 1999; Macher and Boerner, 2012; Bena and Li, 2014; Kerr and Nanda, 2015; Nanda and Rhodes-Kropf, 2017).

Thus, laboratories can manage the R&D resources needed to simultaneously promote innovation in the portfolio of new drugs in two alternative ways. New promising drugs may be developed based on a combination of internal R&D effort and/or financial transactions (external R&D effort). See Figure 1 in Gascón et al. (2017). Our first input (pharmaceutical laboratory internal R&D capability) measures the

internal potential of laboratories to be innovative over time and manage their innovation risk while, our second input, announced NFTs, measures the ability to rearrange the portfolio of new drugs by externally acquiring (and/or selling) new knowledge while keeping greater control of the innovation process than in cooperation arrangements. Thus, financial transactions by pharmaceutical laboratories in order to acquire or sell certain drugs (or laboratory R&D divisions) are an alternative way of managing the portfolio of promising drugs at different stages of the pipeline. They are also a way of acquiring R&D strength or of discarding an R&D line that is no longer strategic and/or efficient See Table A.1 (Appendix A) for detailed information about factors in our model.

2.3. Input variable 3 – Probabilities of success associated with authorized New Chemical Entities

Firms with greater levels of experience in a given therapeutic area (disease or condition area) tend to obtain greater innovation performance than those with little experience (Macher and Boerner, 2012; Garzon-Vico et al., 2016). Thus, two laboratories with similar internal R&D capabilities and similar NFTs may have different success rates in terms of previously approved new drugs and different pipeline risk. Also, different laboratories will tend to make different strategic choices. These laboratories may choose different strategic approaches. We try to capture these strategic arrangements by taking into account previous successes. In our paper, the success of a laboratory is measured in terms of the number and type of authorized NCEs (new drugs in each ATC code per lab) previously approved by EMA or FDA, and we consider this input as a proxy for lower future innovation risk. More successful approvals imply that the laboratory had the required knowhow and knowledge to successfully bring a new drug to the market, which reduces innovation risk and/or accelerates drug development approval. After identifying NCE approvals by EMA and/or FDA in our sample of pharmaceutical laboratories, and with the aid of our experts, we link drug success information with estimates of average probability of success from phase I to approvals in different ATC codes (classification of therapeutic areas). See Tables A.2 and A.3 (Appendix A) for the probabilities of success from phase I to approval for different ATC codes.

2.4. Input variable 4 – Probabilities of success of Clinical Trials in phases I to IV

As indicated by Khanna et al. (2015) and Garzon-Vico et al. (2016), when successful drug approvals are considered without taking failures into account, a core part of learning and the innovation risk picture is

missed. In order to account for the probability of failures and the portfolio of promising drugs in different pipeline phases, with the aid of experts, we combine information from CTs and conditions (disease areas linked to ATC codes) with information regarding the probability of success from a given phase to approval of each CT. See Table A.4 (Appendix A) for the association of Clinicaltrials.gov conditions (disease areas) with ATC Codes.

Our fourth input are Clinical Trials (CTs) from our sample of pharmaceutical laboratories in phases I to IV during the period 2008 to 2013. CTs provide information of various kinds. In our case, we aim to approximate the innovation risk associated with the strategic choices made by pharmaceutical laboratories when deciding in which therapeutic areas or diseases they would like to be R&D efficient and competitive. By combining these two sources of information, we obtain a picture of the willingness of the laboratory to assume innovation risk in diseases with higher (or lower) probability of success. See Table A.5 (Appendix A) for an association of Clinicaltrials.gov conditions (disease areas) and probabilities of success from the corresponding pipeline phase to approval for each ATC Code.

We try to capture coordination in clinical trials (CTs) by considering two alternative ways of analyzing CTs: (1) focusing only on the main indication (disease or condition) that is being targeted by a given CT; and (2) focusing on a maximum of six main indications (diseases) that are being targeted by a given clinical trial. This second approach captures R&D coordination efforts. Thus, we consider CTs with and without duplications in the targeted diseases. We adjust for CTs which target more than one indication (disease), up to a maximum of six indications (diseases). See Table A.6 (Appendix A).

2.5. Output variable

Drug R&D performance and the variables used to explain this performance vary depending on the approach chosen by those who study the innovation field. Drug performance has been measured in the past as drug approvals, drug R&D submission time or a combination of approvals and failures (Cockburn and Henderson, 2001; Danzon et al., 2005; Macher and Boerner, 2012; Khanna et al. 2015; Garzón-Vico et al., 2016). In our paper, the output variable proposed is the global innovation risk level associated with a given large laboratory based on the assessment assigned to the four above-mentioned input

variables. We have calibrated the fuzzy model and embedded knowledge with the aid of experts in portfolio risk management and in pipeline management.

2.6. Risk evaluation model

With the aim of evaluating global innovation risk, three sequenced evaluation subsystems were generated according to the model structure shown in Figure 1.

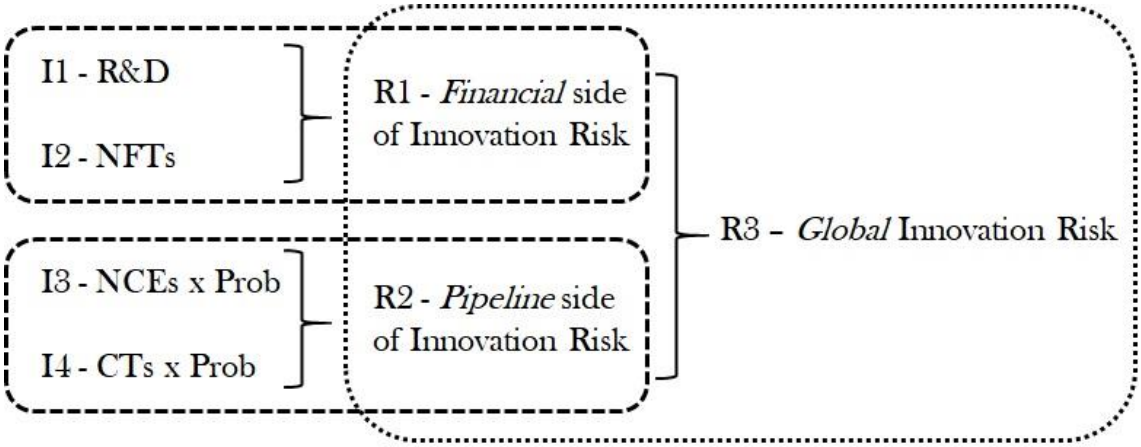


Figure 1. Overview of the proposed risk assessment model.

Note. Considering the financial side of innovation risk, input 1 is R&D expenditure in a pharmaceutical laboratory and input 2 counts the number of announced financial transactions by each pharmaceutical laboratory. See Gascón et al (2017) for more information on how inputs 1 and 2 are calculated. Considering the pipeline side of innovation risk, Input 3 computes, at the laboratory level, the aggregate probability of success of authorized new chemical entities by EMA and FDA adjusting for the disease area of each drug in a given laboratory, and input 4 considers the probabilities of success of clinical trials in a given lab adjusting for the phase and the disease area of each clinical trial. Clinical trials come from the Clinicaltrials.gov website and probabilities come from Thomas et al. (2016).

The first subsystem captures the financial and funding side of innovation risk while the second approximates the pipeline side. The first subsystem determines the financial side of innovation risk of a laboratory (R1) according to the size of its R&D expenditure and the number of financial transactions, NFTs. The second subsystem determines the pipeline side of innovation risk of a laboratory (R2) according to the value of its factors: probability of success of approved NCEs and probability of success of CTs.

We link information on NCEs and CTs with information on the probability of success of drugs in different phases (phase I to approval in the case of authorized NCEs, and phase I to IV to approval in the case of CTs) to approximate pipeline risk. Based on the risk values obtained in these two subsystems,

use of the third subsystem makes it possible to obtain the overall innovation risk associated with each laboratory (R3). In this third subsystem, we allow for two different perspectives, the CFO perspective and the CIO perspective. Figure 1 shows the risk assessment model proposed for a large pharmaceutical laboratory.

Pharmaceutical firms with greater internal and external R&D resources are able to choose between high innovation risk (*growth objective*) and low innovation risk (*stability objective*). Also, larger firms may be sellers or buyers when involved in financial transactions. Smaller firms may have a higher innovation risk or a high probability of being involved in financial transactions as sellers. We try to capture the impact of different strategies on innovation risk.

3. Methodology

One of the main contributions of this paper is of a methodological nature. The methodology aims to evaluate innovation risk in large pharmaceutical laboratories given their strategic choices in four different dimensions (inputs), according to the proposed evaluation model described above.

In order to develop evaluation models such as the one proposed, classical crisp methodologies can be used (e.g. aggregation operators, factor weighting, and regression techniques, among others). However, problems may arise when implementing them because it is difficult to process the intrinsic uncertainty of an evaluation mechanism that is defined by a knowledge base that is consensual and appropriate for the problem being studied (Castro-Lopez et al., 2017). Moreover, various artificial intelligence techniques have proven their suitability in production, service and management areas, helping make decisions and supporting the efficient design of processes and practical applications. Some of these methods may be difficult to apply in the context of this study. For example, the Fuzzy AHP method (Chatterjee et al., 2018) requires finding experts that are able to establish pairwise comparisons of the attributes involved in the model; while the Interval Type-2 Fuzzy Method (Sari et al., 2015) may be difficult to apply by experts from pharmaceutical sector unfamiliar with computer science techniques. Nonetheless, other artificial intelligence techniques, such as the FIS –methodology used in this study to assess the innovation risk of pharmaceutical laboratories – have been successfully applied in multiple fields (medicine, environment, logistics, aeronautics, marketing, banking, among others), which

demonstrates its suitability to manage uncertainty through the appropriate use of natural language and to replicate the reasoning of human beings in the decision-making processes that handle vague and imprecise data (Lin, 2010; Skorupski, 2015; Vadiati et al., 2016; Sardesai et al., 2016).

The use of FIS to assess the innovation risk of pharmaceutical laboratories has various advantages. It facilitates the consensual definition of the input variable ranges of the model and their underlying rating labels. It allows to verify the consistency of the knowledge included in the rule bases agreed by the experts to define the risk assessment procedure. In addition, the use of FIS does not necessarily require a prior normalization of the variables in the model and allows the knowledge necessary to value them to be added in a guided and intuitive manner based on the above mentioned rule bases.

Regarding previous research on innovation in large pharmaceutical firms, the analysis by Garzón-Vico et al. (2016) is close to this study in terms of the sample of pharmaceutical laboratories. However, their methodology (competing risk analysis) and their objective (conditions under which firms' R&D experiences might have stronger or weaker effects on innovation capabilities) are quite different to ours. Tavana et al. (2015) employ an approach built on multi-step, hybrid, fuzzy, multi-criteria decision making (MCDM). They use two fuzzy Data Envelopment Analysis (DEA) models to measure the relative efficiency of large pharmaceutical companies and establish a ranking. We, however, focus on developing an evaluation model that allows us to measure innovation risk.

To the best of our knowledge, there is no other FIS research aiming specifically to assess the innovation risk of pharmaceutical laboratories in a consensual way. However, FIS has been used in similar settings, e.g. to analyze the characteristics of the market for generic pharmaceutical drugs (Gascón et al., 2007; Puente et al., 2011).

3.1. FIS for the evaluation of the proposed model

The definition of a FIS is based on the theory of Fuzzy Sets (Zadeh, 1965). A FIS facilitates management of the uncertainty inherent in the definition of the knowledge needed to evaluate a model, making it possible to represent its functioning in a way that is both realistic and close to human reasoning (Lootsma, 2013). In these systems, the model variables are defined linguistically, and their values are

associated with ordered concepts (e.g. "low", "medium" and "high"); this differs substantially from classical variables whose values are exclusively numerical (Driankov et al., 1996). In the proposed model, the way a level of innovation risk is determined (depending on different levels of its independent variables) may be subject to a high degree of uncertainty. Treating the variables in a linguistic way simplifies the definition of the evaluation criteria given by the experts. In addition, as will be shown below, the interpretation of knowledge for risk assessment that is embedded in the FIS is very intuitive.

The FIS knowledge bases have been defined according to the expert knowledge that we gained on innovation risk assessment. To this end, we have worked closely with three experts/groups of experts, who played different roles in shaping and validating our fuzzy evaluation model, given their diverse backgrounds. In more detail, these are: (i) a PhD in Biochemistry; (ii) a manager with large experience in the pharmaceutical industry; and (iii) a group of academics specialised in financial management and value creation. In the development of our work, we have had periodic meetings with the team of experts. Their individual roles are discussed below. We do not reveal their names for confidentiality reasons.

First, the PhD in Biochemistry expert helped us combine knowledge on authorised new chemical entities (NCEs) and Clinical Trials (CTs) with information on success probabilities for different diseases (conditions) and ATC codes. In this sense, his/her knowledge of the disciplines of biochemistry and pharmacology has been very useful when constructing the knowledge base and when linking coherently the different datasets. Second, the expert in the pharmaceutical sector works currently as a manager in sales and market access in a company operating in the pharmaceutical sector in the North of Spain. His/her current tasks include the promotion of new projects within the company (intra-entrepreneurial activities) that create value for doctors and hospitals. In this sense, his/her knowledge about competition among pharmaceutical laboratories and about publicly available information regarding the marketing of existing and potential new drugs launched by competitors has been extremely useful when embedding the knowledge regarding the pipeline side of innovation risk as well as when seeking the validation of the model. Third, our group of experts in financial management and value creation are colleagues that work at the University of Oviedo, Autonomous University of Madrid, and University of Valladolid. Our colleagues helped us embedding the knowledge related to portfolio risk management and the financial part of innovation risk.

The FIS knowledge base is defined based on the expert knowledge gained on innovation risk assessment. We therefore decided to define three FIS sequenced according to the proposed model. Each subsystem assigns a level of innovation risk based on the levels of two input variables. To design the structure of the inference systems, we adopt the following premises:

(1) To homogenize the problem, the experts first agreed to establish the same number of labels for all the input and output variables of the different subsystems. After considering three options (three, five and seven levels), through the mode of expert evaluations, it was decided to use three levels for the input variables (Low, Medium, High) and five levels for the output variables (Very Low, Low, Medium, High, Very High). Interestingly, this structure makes the rule bases not too wide (9 rules) and provides sufficient discrimination in the assignment of output labels to the said rules. As we will discuss latter, this fact causes certain model variables (in particular, R1 and R2) to have different partitions depending on whether they are treated as inputs or outputs in the relevant subsystems.

(2) For the purpose of semantic representation, we use triangular or trapezoidal labels, which many authors consider sufficiently robust to represent the vagueness of the linguistic evaluations of the considered sources of information (Delgado et al., 1992). Additionally, we use strong fuzzy partitions (Casillas et al., 2003) because they have good properties for comprehensibility and meet important semantic constraints like distinguishability, normalization, coverage or overlapping (Mencar and Fanelli, 2008).

Adopting these premises facilitates the consensual definition of both, the variable partitions and the rule bases of the proposed FIS. Thus, we have adopted a symbolic translation method based on 2-tuples to partition the variables, inspired by the work of Herrera and Martinez (2000). This methodological approach allows us to reach an agreement on the basis of the judgement of several experts regarding different structural alternatives of the label cores assigned to each variable. Each 2-tuple (s_i, α_i) represents linguistic information of the degree of agreement of an expert with different alternatives of cores, with s_i being a fuzzy term of linguistic preference from an original set of fuzzy terms S, and α_I, a value within the interval [-0.5 , 0.5), representing the symbolic translation. The considered original set of fuzzy terms, S, is displayed in Table 1.

Table 1. Original set of fuzzy terms of linguistic preference assignable to each core structure.

	Label		*Trapezes*			
S_0	D	(Disagreement)	0	0	0.3	0.4
S_1	P	(Parcial Agreement)	0.3	0.4	0.4	0.7
S_2	T	(Total Agreement)	0.4	0.7	1	1

By way of illustration, Figure 2 includes four alternative core structures that were proposed for the input variables R&D and NFT, in the first subsystem —it would also be possible to propose alternative cores for each label of the partition individually-.

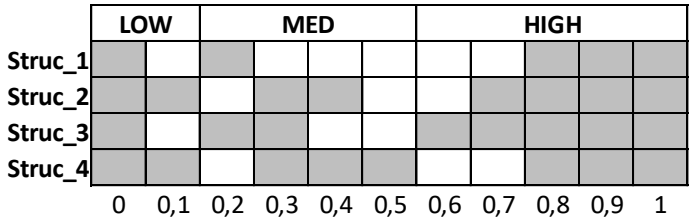


Figure 2. Alternative core structures for the variables R&D and NFT.

The assessments made by our team of experts for these four structures are represented in Table 2.

Table 2. Expert fuzzy evaluations for different core structures.

	Struc_1	Struc_2	Struc_3	Struc_4
Exp1	T	P		
Exp2	P			T
Exp3	T	P	P	
Exp4	P	T		
Exp5		P		T
Extended Average	1,2	1	0,2	0,8
2-tuples:	(P, 0.2)	(P, 0)	(D, 0.2)	(P, -0.2)

Note. We use empty space for the evaluations related to the label 'D-disagreement'.

To reach an agreement on the evaluation of the different experts with respect to each structure, we averaged the orders of their assigned fuzzy terms (*Extended average*). For example, EA (Struc_1) = (0 * 1 + 1 * 2 + 2 * 2) /5 = 1.2. Next, these values were transferred, through a symbolic translation, to their related 2-tuples in the interval [-0.5, 0.5). These 2-tuples measure the consensual preference label and its displacement with respect to the original set of preferences (either to the left or to the right). Figure

3 illustrates this process for the previous value of Struct_1. Subsequently, the core-structure with the highest aggregate preference according to its lexicographical disposition (in this case, "Struc_1") is selected. Finally, taking into account this selected core structure, and considering that the partition needs to be strong, the final semantic of each partition is obtained by central symmetry between every two consecutive labels.

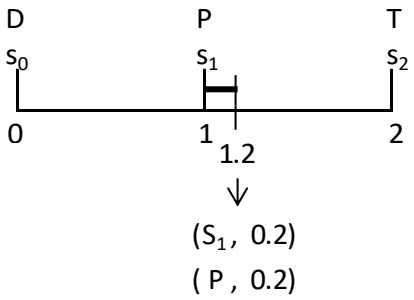


Figure 3. Symbolic correspondence of EA=1.2 with 2-tuple=(P, 0.2).

Figure 4 illustrates the partition obtained for the input variables of the first subsystem.

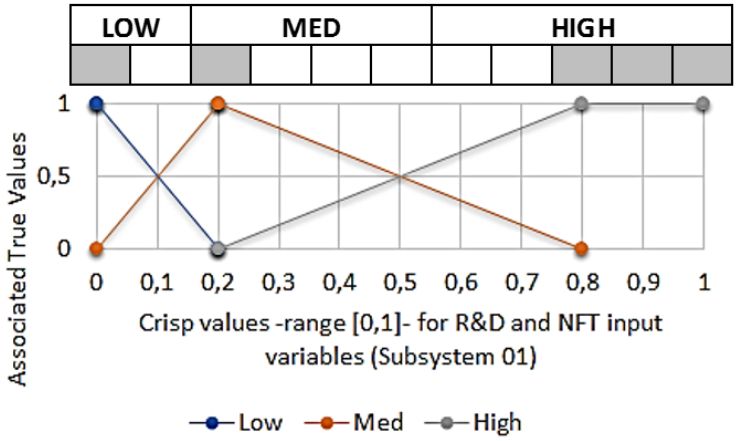


Figure 4. Consensual partition for the variables R&D and NFT.

Figure 5 shows the agreed partitions for the input and output variables for all the FIS subsystems of the proposed model employing this procedure.

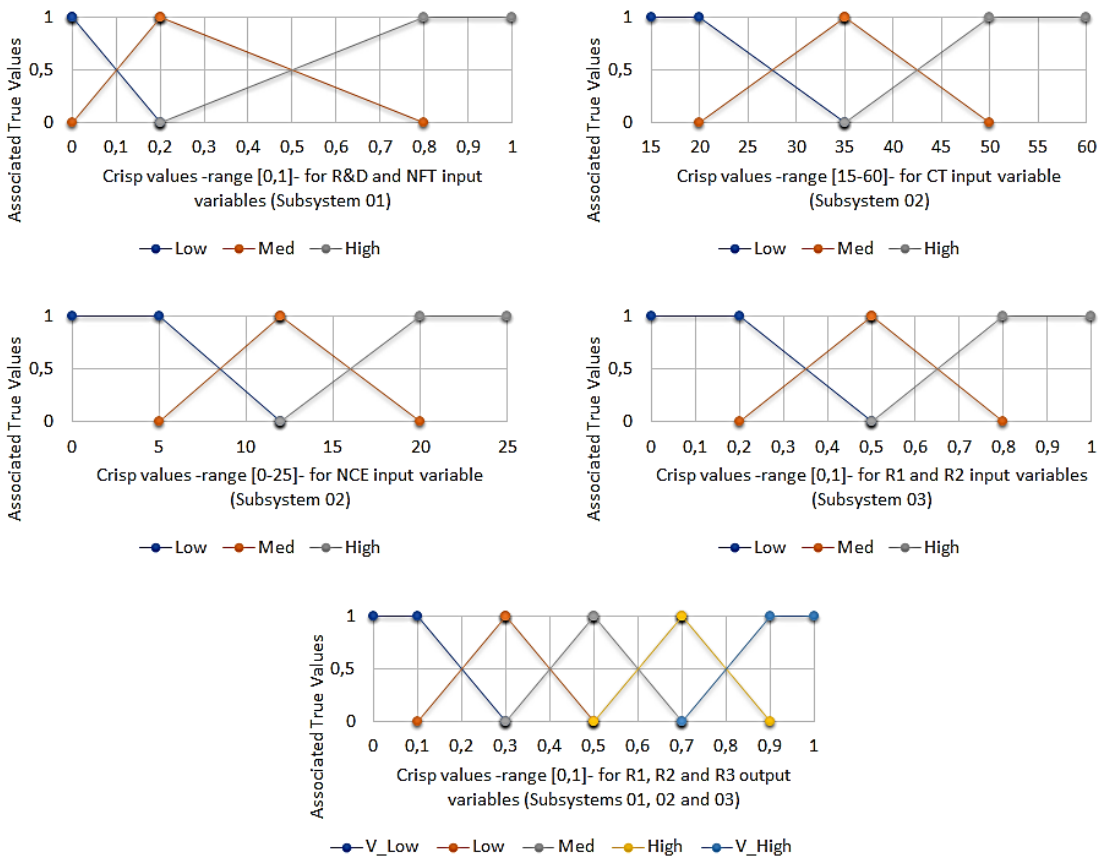


Figure 5. Defined partitions for all the input and output variables in the risk evaluation model.

To define the rule bases, we used the same 2-tuple methodology. Therefore, the experts assess their degree of agreement with respect to the assignment of each possible output label in all the rules. Then, by means of the translation to 2-tuples of the averaged valuation for each potential output label, it is selected in each rule the one that provides the highest degree of acceptance. Figure 6 shows the rule bases obtained using this method for the three subsystems (the third subsystem shows two different rule bases, the first from the point of view of the CFO and the second from the point of view of the CIO).

As an example, the third rule for the determination of financial risk (R1) would be understood as [*If R&D is Low and NFT is High, then R1 is High*].

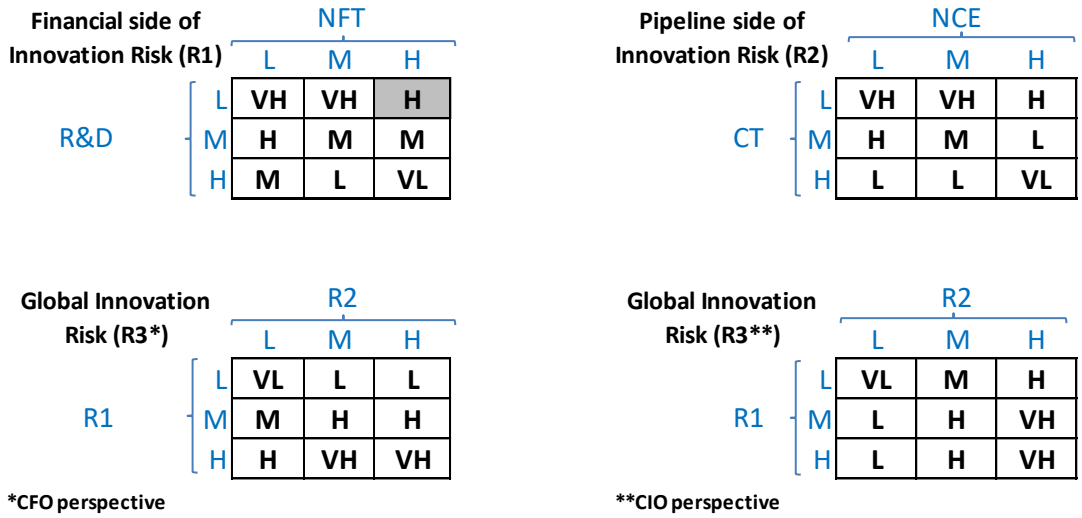


Figure 6. Rule bases for the three defined fuzzy subsystems.

3.2. Mamdani Inference: Study of inference surfaces for the subsystems of the model

Relying on everything defined above, Mamdani-type FIS trigger the inference process given the crisp values of the four input variables of the proposed model. These FIS seek to infer a crisp numerical value for each output variable as a function of the crisp values given to their corresponding input variables. This process consists of five main stages (Mamdani and Gaines, 1981): (1) fuzzification; (2) application of logical operators in every rule's antecedent; (3) implication in every rule's consequent; (4) aggregation of all rules' consequents; and (5) defuzzification of the final aggregate.

First, these crisp input values are fuzzified, which refers to their conversion from real to truth values, between 0 and 1, according to the labels intercepted in the corresponding partitions in all the rules. Second, by applying appropriate operators to these intercepted values in the antecedent of each rule —following the logical connectives that link its variables—, a global truth value for each rule is calculated. We note that the "min" operator is commonly considered for the "and" connector. Third, the global truth value of a rule (activation level) is transmitted to its consequent in the implication stage. It is generally generated by truncating the label of its output variable to that activation level. Next, the truncated output labels of all active rules are grouped in the aggregation stage (commonly overlapping them and choosing the path of maximum truth values). Finally, the aggregated fuzzy set must be defuzzified to obtain the final crisp value of the output variable, usually by calculating the abscissa of its centre of gravity.

By way of example, Figure 7 illustrates the inference process of the initial subsystem, labelled as RiskPham1, for the laboratory "Bayer" (whose normalized input crisp values are R&D=0.51 and NFT=0.43). In this figure, each row represents a rule in the said subsystem, while the final block of the last column represents the final aggregate whose center of gravity (abscissa) will be the risk R1 that we obtained for the laboratory. First, we fuzzify the aforementioned crisp values in the input variables of all the rules, obtaining the truth values shaded in the first two columns (i.e., partial activation levels). Second, and given that "AND" is the logical connector in the antecedent of the rules, the global activation level of each rule is obtained as the minimum of the partial activation degrees of its input variables —consequently, in this examples, only rules 5, 6, 8, and 9 are activated. Third, the implication to the consequents of the activated rules occurs, truncating their output labels to the global activation levels of the previous step (that is, the shaded areas of the last column). Fourth, the aggregation of the truncated labels of all rules takes place by means of the MAX method, which involves the superposition of the truncated labels of all rules and the selection of the path of maxima in the domain of the output variable (shaded area in the last block of the third column). Fifth and finally, the final aggregate of the previous step is defuzzified through the gravity-center method, which leads to obtaining the risk R1 for each laboratory (in this case, 0.38).

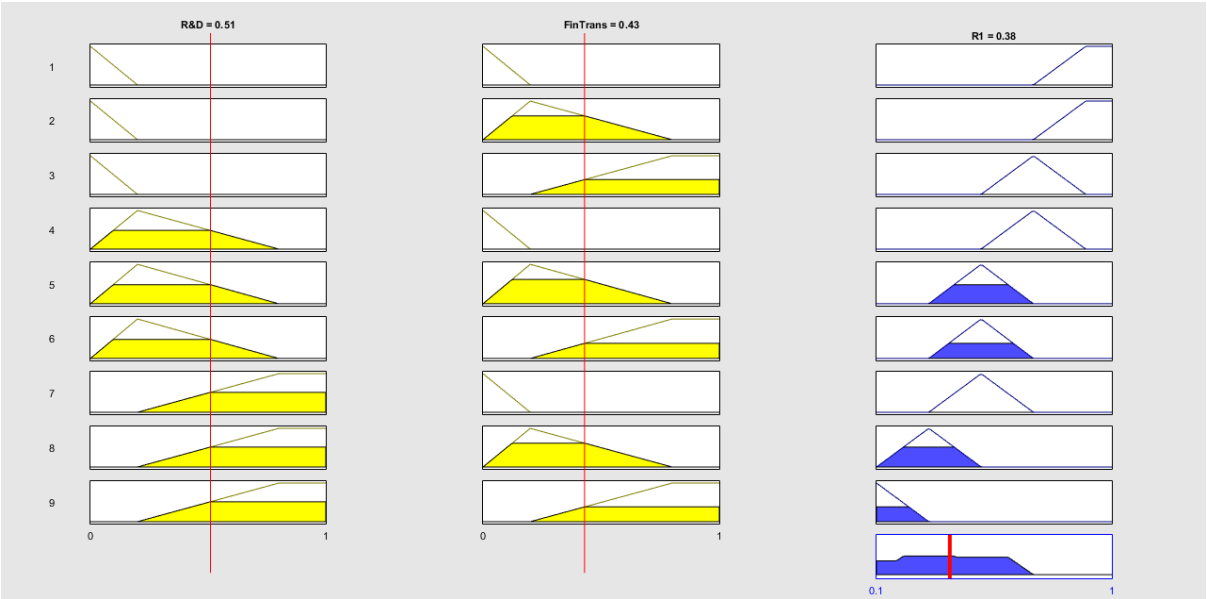


Figure 7. Fuzzy inference process of the initial subsystem, RiskPharm1, for the laboratory "Bayer".

Similarly, the second inference subsystem, named RiskPharm2, operates by considering the crisp values of its input variables, CT and NCE, according to the partitions and rules agreed upon for it. This allows to estimate the risk R2 for each pharmaceutical laboratory. Finally, to determine the Global Innovation Risks (R3 * and R3 **) of the different laboratories, the inference subsystems RiskPharm31 (CFO perspective) and RiskPharm32 (CIO perspective) act on the previously obtained values of risks R1 and R2 —which are interpreted in this case as inputs—, according to the different knowledge bases defined for them.

Although the methodology may appear to be operationally complex, there are multiple software programs that enable researchers to carry out this evaluation process by simply defining the labels associated with the system variables and the rule base that incorporates the decision knowledge. We use the software Matlab fuzzy logic toolbox ® v. 2.0 (Chen and Klein, 1997) to develop our FIS. A detailed explanation of the operation of this software can be accessed from Mathworks Web (http://www.mathworks.com/products/fuzzy-logic/).

In addition, MATLAB allows one to easily concatenate a set of FISs. In this sense, we can evaluate at the same time a wide sample of laboratories. The following code lines illustrates how we have concatenated the three subsystems.

R&D	%Stores the crisp values of the R&D variable for the sample of laboratories%
NFT	%Idem for NFT%
CT	%Idem for CT%
NCE	%Idem for NCE%
Sys1=Readfis(‘ RiskPharm1.fis’);	%Reads the FIS structure that allows us to evaluate R1%
Sys2=Readfis(‘ RiskPharm2.fis’);	%Idem for R2%
Sys31=Readfis(‘ RiskPharm31.fis’);	%Idem for R31 (CFO perspective)%
Sys32=Readfis(‘ RiskPharm32.fis’);	%Idem for R32 (CIO perspective)%
R1=Evalfis([R&D NFT], Sys1);	%Estimates the R1 values for the sample of laboratories%
R2=Evalfis([CT NCE], Sys2);	%Idem for R2%
R31=Evalfis([R1 R2], Sys31);	%Idem for R31 (CFO perspective)%
R32=Evalfis([R1 R2], Sys32);	%Idem for R32 (CIO perspective)%

Note. The .fis files, generated with MATLAB, can be accessed in the online dataset repository.

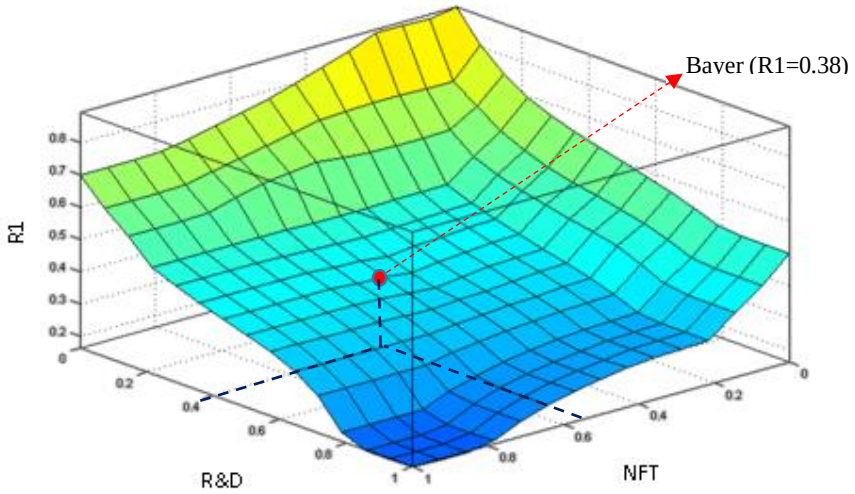
The congruence of the evaluations obtained through the designed FIS can be easily and intuitively investigated through the inference surfaces supplied by each model’s subsystem. These maps represent the scores of the output variables by the height of the surface at each point. By way of example, Figure 8a shows the evolution of the financial risk “R1” evaluation as a function of the “R&D” and “NFT”

values. The risk R1 of each laboratory should lie on the surface we show (by way of illustration, we show the position of the risk R1 for the laboratory 'Bayer' according to the data employed in the inference process previously discussed). The obtained surface proves that the larger the values of R&D and NFT variables, the higher the financial risk "R1", being the gradient more pronounced for the R&D variable. Figure 8b shows the evolution of the innovation risk "R2" evaluation as a function of the "CT" and "NCE" values. Unlike the previous case, we observe how we obtain increasing values of innovation risk for decreasing values of the input variables –as it can be seen in the horizontal axis of the map, corresponding to the variation of the values of these variables CT and NCE-. It is also observed how, according to the knowledge inserted in this system, the variable that causes higher gradients in the level of innovation risk is "TC" —that is, a relatively small decrease in this variable causes significant increases in innovation risk.

Finally, Figures 8c and 8d show the evolution of global risk "R3" as a function of the "R1" and "R2" values, from the point of view of the CFO or the CIO, respectively. Based on the knowledge inserted for determining the global risk, an inverse behaviour is observed between both surfaces, showing the need to achieve a trade-off between the interests of the Financial Management and the Innovation Department.

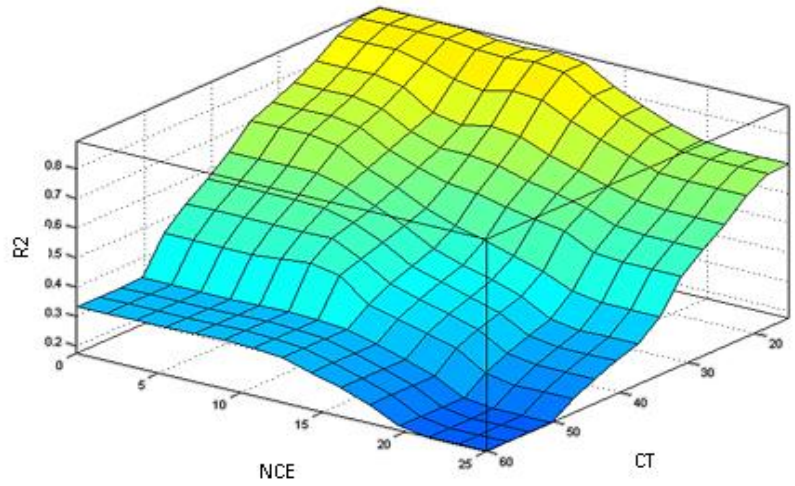
In general terms, fuzzy inference models can be constructed with pre-existing knowledge of the behaviour of the system to be modelled and / or with the knowledge provided by a panel of experts on such behaviour. In the first case, the validation of the rules extracted from pre-existing knowledge is usually carried out by quantifying an error measure —such as the root mean square error (RMSE)— of the outputs given by the model and those provided by the real system. In the second case, generally it is not possible to establish a validation procedure for the rules generated given that the outputs of the real system cannot be known; see e.g. Rigatos and Zhang (2009). In our model, we use "Mamdani" inference rules, which are agreed by experts through an innovative 2-tuple method, that cannot be validated against the innovative risk values of real-world pharmaceutical laboratories due to the lack of published official data. Having clarified this important point, our model has been constructed in a rigorous and consensual manner (with the important contribution of the expert team). Moreover, in all cases, these surface maps were shown to the experts who allowed us to reach an agreement on the knowledge base. They showed

a high degree of acceptance with respect to the global behaviour defined by the maps and suggested to evaluate and discuss the results of the model according to the data of 31 large pharmaceutical laboratories.



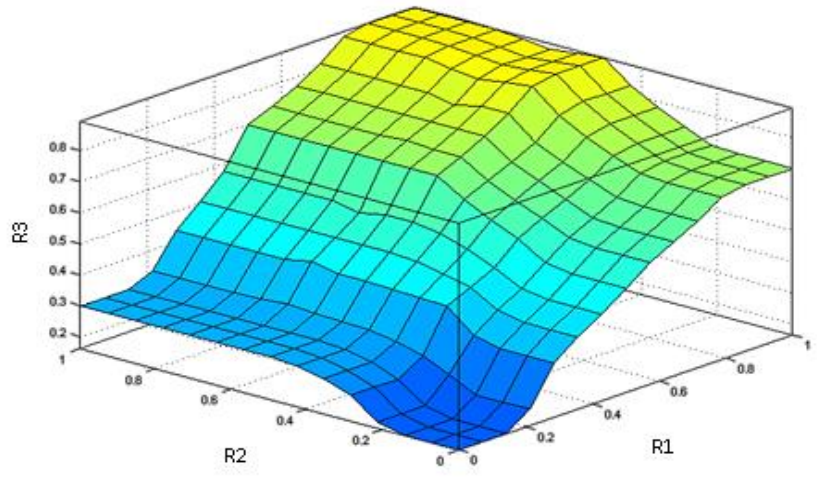
a) Risk R1 from R&D and NFT

Note. Risk R1 captures the evolution of the financial dimension of innovation risk according to the intensity of internal R&D expenditure and according to the number of financial transactions announced by a pharma lab in order to buy and sell other pharmaceutical laboratories.



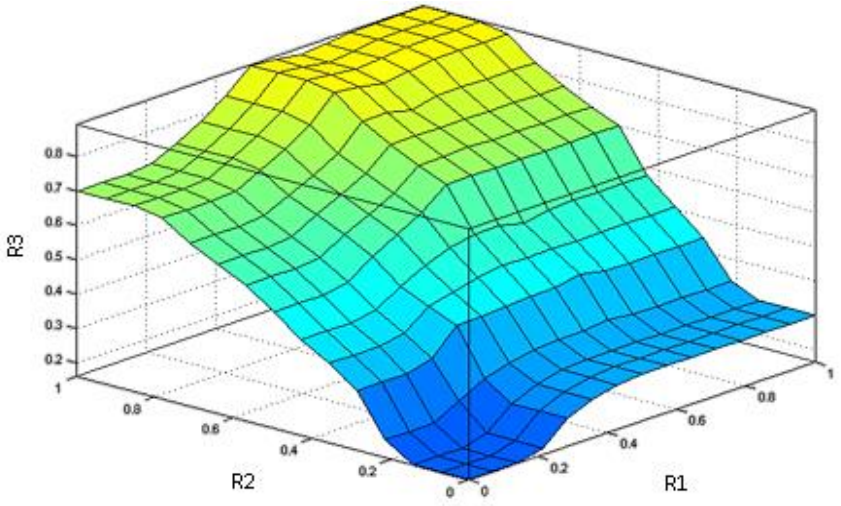
b) Risk R2 from NCEs and CTs

Note. Risk R2 captures the evolution of the pipeline (strategic) dimension of innovation risk according to the number of new chemical entities (NCE) authorized by EMA and FDA and according to an aggregate figure of the number of clinical trials (CT) in the different disease groups and different phases I to IV of clinical trials.



c) Global innovation Risk R3 from R1 & R2 (CFO Perspective)

Note. Innovation risk R3 from a CFO perspective captures the global innovation risk from a Chief Financial Officer perspective where the financial side of innovation risk, R1, is more relevant to the analysis than the pipeline side of innovation Risk, R2.



d) Global innovation Risk R3 from R1 & R2 (CIO Perspective)

Note. Innovation risk R3 from a CIO perspective captures the global innovation risk from a Chief Innovation Officer perspective where the pipeline (strategic) side of innovation risk, R2, is more relevant to the analysis than the financial side of innovation Risk, R1.

Figure 8. Inference Maps for all the fuzzy subsystems of the risk evaluation model.

4. Application of the decision-making system to 31 large pharmaceutical laboratories: Results, evaluation of the model and discussion

Although we obtained intermediate results in the first two subsystems (see Appendix B), we will focus mainly on the results obtained in the third subsystem. The third FIS is a weighted combination of the previous two subsystems, as demonstrated by the very definition of their respective rule base. Depending on the type of user of the fuzzy subsystems, more weight will be allocated to the first subsystem (financial side of innovation risk) or, alternatively, to the second subsystem (pipeline side of innovation

risk). If we are analyzing strategic issues and decision making from the point of view of the CFO, then the first fuzzy subsystem should be assigned a greater weight given that it is the most relevant subsystem for obtaining a global vision of the internal and external R&D budget. Alternatively, if we are analyzing pipeline strategic issues from the point of view of the CIO, then the second fuzzy subsystem should be allocated a greater weight given that it is the most relevant subsystem for deciding in which therapeutic areas (or diseases) and phases I to IV the pharmaceutical laboratory is going to be more active, given previous successful approvals and given the probabilities of success of different drugs depending on the class of disease(s).

Table 3 contains the correlation matrix of the four innovation risk measures (CFO perspective with CT duplications, CIO perspective with CT duplications, CFO perspective without CT duplications and CIO without CT duplications). As expected, there is a very high correlation (almost 100% in one case and 97% in the other) between both CFO perspectives (with and without CT duplications) and between both CIO perspectives (with and without CT duplications). This implies that there are no major differences between the estimation innovation risk using CTs with duplications or CTs without duplications.

Table 3. Correlation matrix of the four innovation risk measures

	CFO CT dup	CIO CT dup	CFO CT nodup	CIO CT nodup
CFO CT dup	1.0000	-	-	-
CIO CT dup	0.6137	1.0000	-	-
CFO CT nodup	0.9962	0.6111	1.0000	-
CIO CT nodup	0.6141	0.9745	0.6296	1.0000

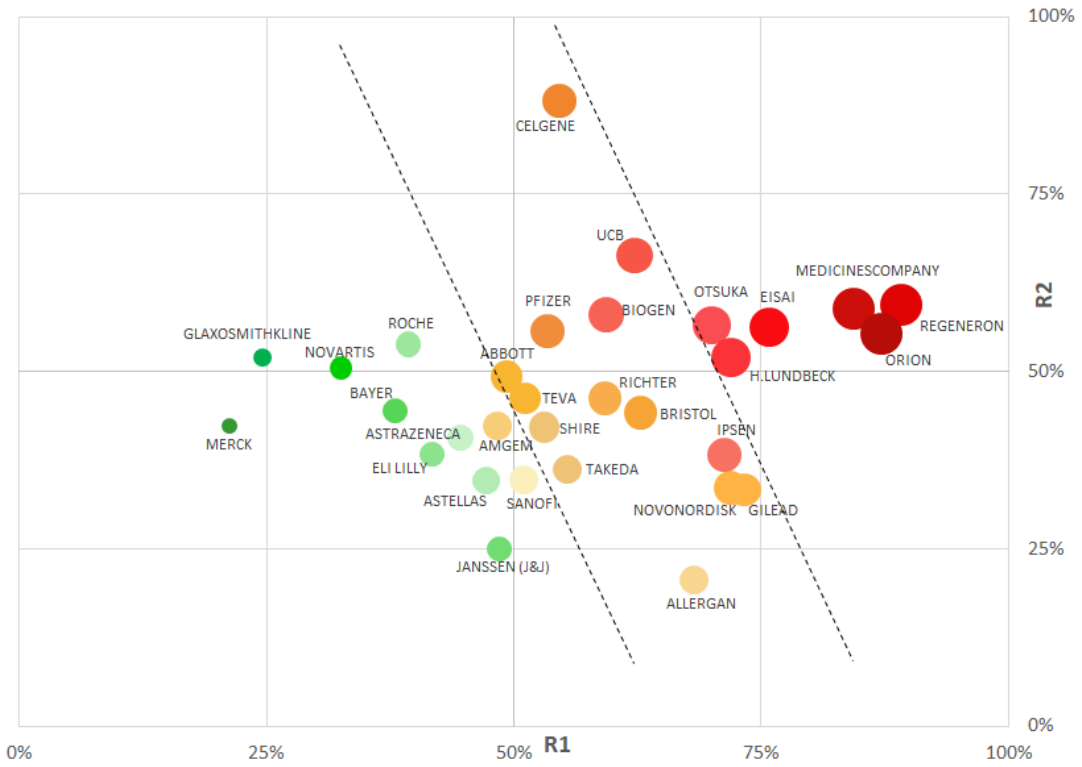
Note. CFO stands for Chief Financial Officer and CIO stands for Chief Innovation Officer. CT no dup is our acronym for the main indication (targeted disease) of each clinical trial while CT dup is our acronym when we consider a maximum of six main indications (targeted diseases) that are being targeted simultaneously by a given clinical trial. CFO CT dup and CIO CT dup are the CFO and CIO perspectives with CT duplications. CFO CT nodup and CIO CT nodup are the CFO and CIO perspectives without CT duplications.

We try to capture this coordination by considering two alternative ways of analyzing CTs: (1) focusing only on the main indication (disease) that is being targeted by a given CT; and (2) focusing on a maximum of six main indications (diseases) that are being targeted by a given clinical trial. This second approach captures research coordination efforts. Thus, we consider CTs with and without duplications in the targeted diseases. We adjust for CTs which target more than one indication (disease), up to a maximum of six indications (diseases). However, the correlation between the CFO perspective with CT

duplications and the CIO perspective with CT duplications is 61% while the correlation between the CFO perspective without CT duplications and the CIO perspective without duplications is also 61%. Given these results, we suggest that the CFO perspective and the CIO perspective capture different aspects of innovation risk.

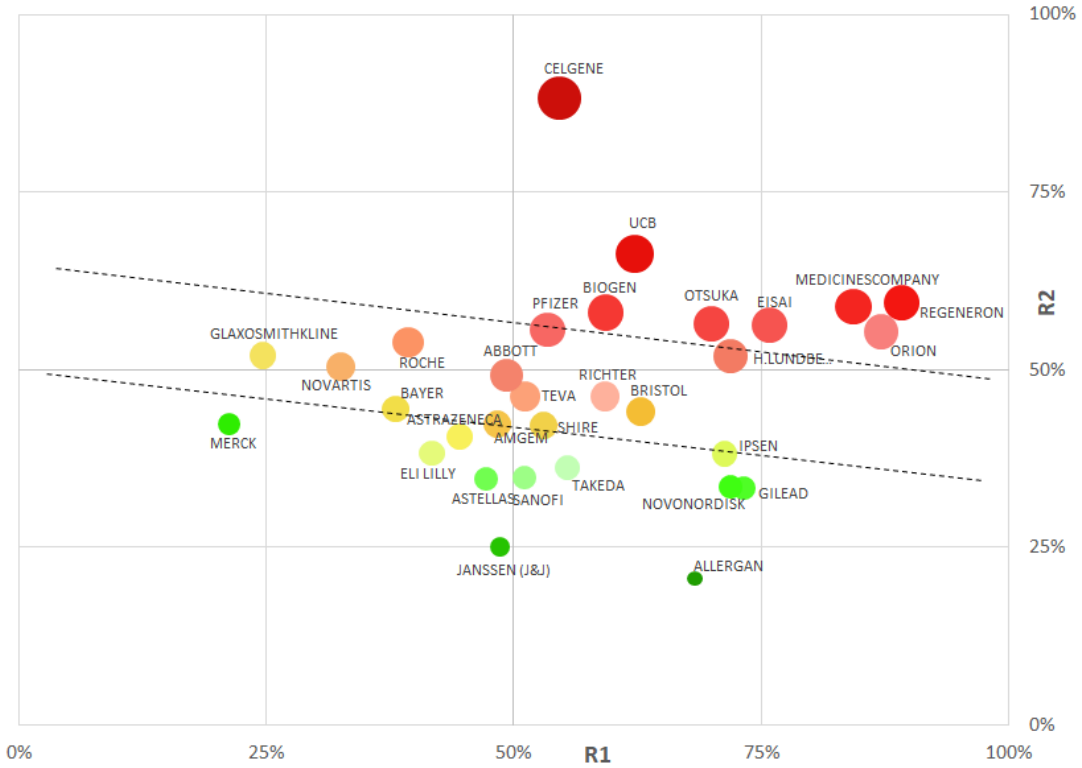
In order to interpret our results, it is important to note that high (low) innovation risk is not bad per se. There may be low-innovation-risk laboratories that create (destroy) value, or high-innovation-risk laboratories that also create (destroy) value. With the aim of better understanding these results, Figure 9 illustrates the global innovation risk associated with the 31 firms that we considered for CTs with and without duplications from the perspectives of both the CFO (Figures 9a and 9c respectively) and the CIO (Figures 9b and 9d respectively). The axes of both figures show the level, in percentage terms, of risk R1 and R2 obtained by the 31 laboratories in the two initial fuzzy subsystems, while the area of the circles represents the level of global risk R3 for each laboratory. Moreover, for the purposes of better visualization, the risk level of each laboratory (circle) has been associated to a color scale that ranges from bright green (low global innovation risk) to bright red (high global innovation risk) through a range of oranges (intermediate innovation risk).

Figures 9a and 9c illustrate how an increase in the level of risk R1 translates into a more significant increment in global risk when seen from the CFO perspective. From this viewpoint, for the period of analysis that we consider, the firms with lower global innovation risk are Merck, Glaxosmithkline, and Novartis, while the laboratories with higher global innovation risk are Medicines Company, Orion, and Regeneron. On the other hand, global innovation risk is more sensitive to an increase in the level of risk R2 from the perspective of the CIO, as can be seen in Figures 9b and 9d. In this case, the pharmaceutical firms with lower global risk are Allergan, Merck, and J&J, while those with higher global risk are MedicinesCompany / Regeneron (the former if we consider duplications, the latter if we do not), UCB, and Celgene.



a) Innovation Risk from the CFO perspective (without CT duplications)

Note. CFO stands for Chief Financial Officer. CT without duplications imply that we consider only the main indication (targeted disease) of each clinical trial. R1 and R2 are the two dimensions of innovation risk. See Figure 1.

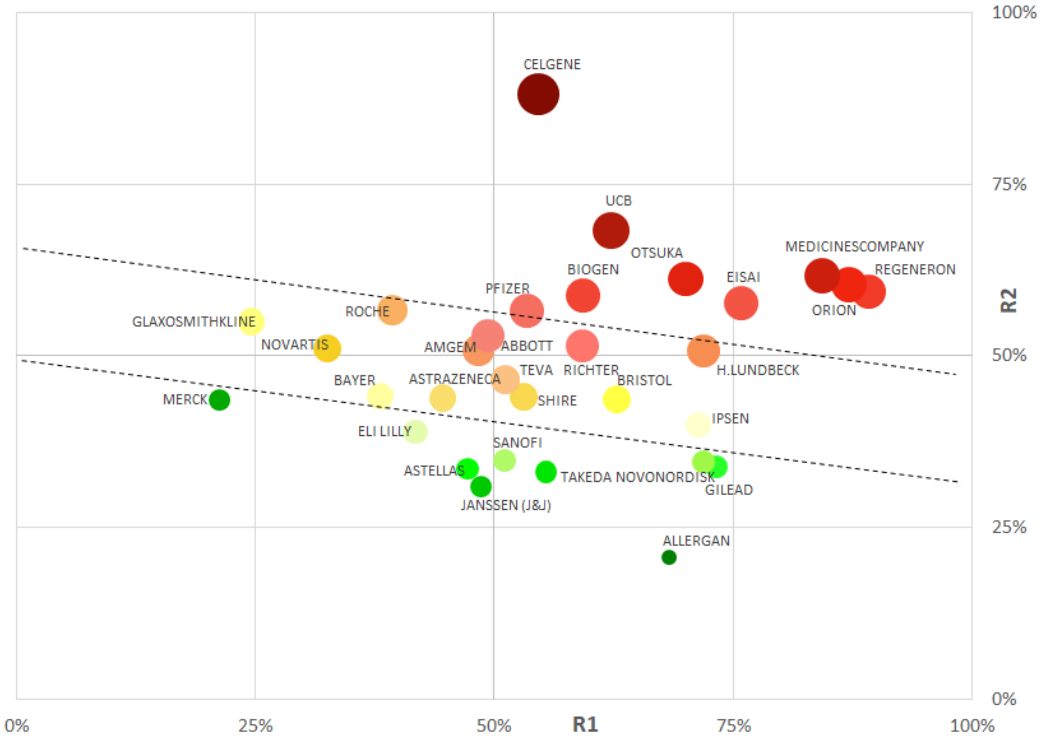


b) Innovation Risk from the CIO perspective (without CT duplications)

Note. CIO stands for Chief Innovation Officer. CT without duplications imply that we consider only the main indication (targeted disease) of each clinical trial. R1 and R2 are the two dimensions of innovation risk. See Figure 1.

c) Innovation Risk from the CFO perspective (with CT duplications)

Note. CFO stands for Chief Financial Officer. CT with duplications imply that we consider a maximum of six main indications (targeted diseases) that are being targeted simultaneously by a given clinical trial.R1 and R2 are the two dimensions of innovation risk. See Figure 1.



d) Innovation Risk from the CIO perspective (with CT duplications)

Note. CIO stands for Chief Innovation Officer. CT with duplications imply that we consider a maximum of six main indications (targeted diseases) that are being targeted simultaneously by a given clinical trial.R1 and R2 are the two dimensions of innovation risk.. R1 and R2 are the two dimensions of innovation risk. See Figure 1.

Figure 9. Global Innovation Risk of the 31 pharmaceutical laboratories analyzed.

Figure B.1, in Appendix B, shows the R1 and R2 risks for the pharmaceutical laboratories that we cover in this research work.

Regarding the interpretation and possible alternative ways of using our evaluation model and our results (shown in the two-dimensional graphs of our third FIS), the reader should bear in mind that we include financial information in the first FIS (R&D expenditure and financial transactions) and pipeline risk information in the second FIS (probabilities of success of both new authorized molecules and clinical trials). Given our four inputs in the model, we are not in a position to use new chemical entities (NCEs) and clinical trials (CTs) as drug pipeline data in order to evaluate the third FIS (nor can we use R&D expenditure and the number of announced financial transactions per lab (NFTs) to evaluate this third fuzzy subsystem).

Augusiak et al. (2014) coin the term "evaludation", merging the concepts of validation and evaluation. Evaluation is a more neutral term than validation. They consider six elements of "evaluation" in their modelling cycle[1] that we have followed in order to be systematic when evaluating our model.

In order to evaluate our model, we showed our graphs to the same experts in the pharmaceutical field that helped us to establish the rules of the model to request their impressions regarding its results[2]. Special attention was given to the comments, insights and impressions given by the expert from a large pharmaceutical laboratory (whose company is not part of our sample of pharmaceutical laboratories). These experts indicate that, with our model, it is possible to compare firms with high risk that are located in different regions of the bi-dimensional risk graph. For example, Celgene is a risky laboratory with higher CFO risk than Regeneron while Regeneron has a higher CIO risk than Celgene. Celgene is more oriented towards rare diseases and diseases with higher pipeline risk but it has a sounder financial position than Regeneron which is a smaller biotech lab.

[1] We follow the modelling cycle specified by Augusiak et al. (2014). Given our sources, we are sure about the quality of our data, and we think that our four inputs capture innovation risk in a simple but effective manner. Our equations and the fuzzy software are valid in our approach. Regarding model analysis, we explore sensitivity to changes in parameters considering CTs with and without duplications. Regarding model output corroboration, we contacted experts in order to share our output results and also ran regressions including new data that were not used during the development of our model and model parametrisation.

[2] Regarding the construction of the rules of the model, we combined our own experience in the pharmaceutical field with the expertise of outside experts. In particular, we contacted a person from a pharmaceutical laboratory that it is not in our sample and a person with a PhD in Biochemistry with no current links to any pharmaceutical laboratory and no conflict of interest regarding our study.

With the aim of evaluating our model using different approaches, we identified some additional variables that were not used in our fuzzy model and are useful for evaluating our model results.

We ran a series of Ordinary Least Squares (OLS) regressions with bootstrap (500 replications) robust standard errors that we show in Appendix C, where the dependent variable is a variable that was not used as an input in the fuzzy model but may be related to innovation risk, such as sales or debt[3]. We use instrumental variables in order to better account for endogeneity and causality issues. See also the correlation matrix in Table 4.

Table 4. Correlation matrix.

	Avg Sales	Sales Rat.	Avg Debt	Debt Rat.	Avg Ta.	Avg MCap
Avg Sales	1.0000	-	-	-	-	-
Sales Rat.	-0.2361	1.0000	-	-	-	-
Avg Debt	0.8654	-0.3768	1.0000	-	-	-
Debt Rat.	0.2708	-0.2278	0.5388	1.0000	-	-
Avg Ta.	0.9144	-0.4457	0.8871	0.2015	1.0000	-
Avg MCap	0.8893	-0.3317	0.7636	0.1754	0.8889	1.0000

Note. The average of each variable is calculated in the period 2008 to 2013 which is the same time period that is used in order to calculate innovation risk. Avg Sales are average sales of each pharmaceutical laboratory in the period 2008 to 2013. Sales Rat. is the ratio of sales to total assets in the same period. Avg Debt is the average debt while Debt Rat. is the ratio of debt to total assets. Avg Ta. is average total assets and Avg Mcap is the average market capitalization in the period 2008 to 2013. See appendix C for additional regressions using lagged values as instruments.

Regarding sales, the following Table 5 shows OLS results where average sales (or average sales to total assets in the period) are the dependent variable and CFO and CIO innovation risk are the two independent variables. CFO innovation risk is significant at the 1% level when the dependent variable is average sales in the period 2008 to 2013, but CIO innovation risk is not significant. The coefficient of CFO is negative although very close to zero. When the dependent variable is the ratio of sales to total assets in the period 2008 to 2013, CFO innovation risk is significant at the 10% level but CIO innovation risk is not significant. The coefficient of CFO is positive in this case. Thus, after adjusting for size (dividing by average total assets), the coefficient changes.

[3] We consider average sales in the period 2008 to 2013 as well as the ratio of sales in the period to average total assets in the period. We also consider average debt in the period as well as the ratio of average debt to average total assets in the period. The variable of sales (or debt) also captures the size of the pharmaceutical laboratory. In order to adjust for size, we divide sales (or debt) by average total assets in the period.

Regarding debt, Table 6 shows OLS results where average debt (or average debt to total assets over the period) is the dependent variable and CFO and CIO innovation risk are the independent variables. CFO innovation risk is significant at the 1% level when the dependent variable is average debt in the period 2008-2013, and CIO innovation risk is significant at the 10% level. The CFO coefficient is negative and the CIO coefficient is positive, both being very close to 0. When the dependent variable is the ratio of debt to total assets in the period 2008 to 2013, CFO innovation risk is significant at the 10% level but CIO innovation risk is not significant. The CFO coefficient is negative in this case. Thus, after adjusting for size (dividing by average total assets), the coefficient does not change. Given our results, more debt (a higher debt ratio) is associated with lower innovation risk (or vice-versa, as we are not inferring causality, see Appendix C).

By using OLS regressions we tried to assess the relevance of innovation risk for explaining debt (ratio) in Table 6, and also for explaining sales (ratio) in Table 5. We also ran additional regressions with total assets (or market capitalization). Results are similar to those in columns (i) and (ii) of Tables 5 and 6. This is not surprising, given that average sales, average debt, average total assets and average market capitalization are different proxies for size. See Appendix C for further regressions with instruments (lagged values) to better account for endogeneity issues.

One alternative approach to further evaluate and/or validate our model may be to use additional public and/or private (proprietary data) from the laboratories in our sample.

Though the methodology is applied to 31 large pharmaceutical laboratories, it is also applicable to, and valid for, other pharmaceutical laboratories. The sample of 31 large pharmaceutical firms comes from the sample of 37 laboratories in Gascón et al. (2017). The overall risk results offered by our Inference System in these 31 laboratories can be seen in Table D.1 (Appendix D) (outputs of the third fuzzy subsystems both with and without duplications in the CTs).

Table 5. Summary of the results of the regression models with sales as the dependent variable.

	Avg Sales (i) CT dup	Avg Sales (ii) CT no dup	Sales ratio (iii) CT dup	Sales ratio (iv) CT no dup
CFO CT dup	-1.14e+08***		.612*	
	(2.04e+07)		(0.342)	
CIO CT dup	2.89e+07		-0.542	
	(2.94e+07)		(0.363)	
CFO CT nodup		-1.14e+08***		0.622*
		(1.98e+07)		(0.332)
CIO CT nodup		3.01e+07		-0.532
		(3.22e+07)		(0.326)
Constant	7.87e+07***	7.80e+07***	0.537***	0.519*** (0.177)
	(1.61e+07)	(1.45e+07)	(0.193)	
R-squared	0.489	0.493	0.135	0.134
No. observations	31	31	31	31

Note. The dependent variable in each regression is average sales in (i) and (ii) and the ratio of sales to total assets in (iii) and (iv). CFO CT dup and CIO CT dup are the CFO and CIO perspectives with CT duplications. CFO CT nodup and CIO CT nodup are the CFO and CIO perspectives without CT duplications. All variables (innovation risk as well as sales and sales ratio) are calculated in the period 2008 to 2013. See appendix C for additional regressions using lagged values of sales. In addition, *, **, *** indicate significance at the 1, 5 and 10% levels. Bootstrap Standard errors in parentheses.

Table 6. Summary of the results of the regression models with debt as the dependent variable.

	Avg Debt (i) CT dup	Avg Debt (ii) CT no dup	Debt ratio (iii) CT dup	Debt ratio (iv) CT no dup
CFO CT dup	-5.78e+07***		-0.363*	
	(9.95e+06)		(0.205)	
CIO CT dup	3.14e+07*		0.365	
	(1.63e+07)		(0.236)	
CFO CT nodup		-5.68e+07***		-0.344*
		(9.82e+06)		(0.204)
CIO CT nodup		2.96e+07*		0.325
		(1.75e+07)		(0.227)
Constant	2.75e+07***	2.82e+07***	0.208*	0.224**
	(6.66e+07)	(6.99e+07)	(0.109)	(0.105)
R-squared	0.429	0.420	0.149	0.123
No. observations	31	31	31	31

Note: The dependent variable in each regression is average debt in (i) and (ii) and the ratio of debt to total assets in (iii) and (iv). CFO CT dup and CIO CT dup are the CFO and CIO perspectives with CT duplications. CFO CT nodup and CIO CT nodup are the CFO and CIO perspectives without CT duplications. All variables (innovation risk as well as debt and debt ratio) are calculated in the period 2008 to 2013. See appendix C for additional regressions using lagged values of debt. In addition, *, **, *** indicate significance at the 1, 5 and 10% levels. Bootstrap Standard errors in parentheses.

5. Conclusions

Our fuzzy evaluation model can be interpreted as a useful tool to evaluate the impact of a portfolio of "local" decisions, i.e. at an individual trial level, on the "global" innovation risk, i.e. considering the whole organisation. In this sense, it allows decision makers to evaluate their potential, or future, innovation risk under different strategies; thus allowing for beneficial what-if analyses of how innovation risk is affected by strategic changes in the portfolio of clinical trials. This information would help managers at different decision levels take better strategic decisions regarding the management of their present and future portfolio of clinical trials in an uncertain environment, in the profit of not only themselves but also the wider healthcare industry. In summary, our fuzzy model enhances strategic decision making at pharma labs by comparing the present innovation risk scenario of a pharma lab relative to its competitors (embedding knowledge based on a given portfolio of clinical trials, on prior success and on a given R&D budget). In addition, managers will better understand what would happen in the long term to the pharma lab innovation risk if alternative strategic changes in the portfolio of clinical trials are proposed or implemented.

We would like to note that our fuzzy evaluation model assess innovation risk at large pharmaceutical laboratories by integrating information from different publicly available sources. For this reason, given that we provide the necessary tools and datasets, new analyses can be easily performed. Also, this model provides a framework that is useful to explore and provide valuable insights on the link between R&D strategy and innovation risk at pharmaceutical companies.

The application of fuzzy methodologies to the healthcare industries has been proposed recently by several authors. For example, Albino et al. (2018) and Nakawala et al. (2018) employ this approach to improve process and enhance training at hospitals. A different line of research is that by Carlsson et al. (2007) and Lo Nigro et al. (2016), which suggest the usefulness of fuzzy techniques to optimize the R&D portfolio. Guo et al. (2018) highlight that it is fundamental to appropriately balance strategic and financial issues when figuring the composition of the R&D portfolio in a pharmaceutical laboratory. They combine fuzzy techniques with a real options approach. In order to validate the model with a real

case, they apply it to a single, relatively small and unknown Chinese pharmaceutical company, which every year selects a specific number of projects (around 30) to implement from 100 candidate projects.

In this paper, after consulting experts in the field with different profiles, we develop a fuzzy evaluation model that helps managers at R&D intensive pharmaceutical laboratories take strategic decisions by capturing the innovation risk of the R&D portfolio *of clinical trials*. Our approach allow them to compare the innovation risk of a specific laboratory with the innovation risk of competitors. It also enables managers to visualize simultaneously the financial and strategic sides of innovation risk. The model that we propose in this work is based on an innovative 2-tuple method, which allows to reach an agreement in both the fuzzy labels of the partitions of the relevant variables and the rules embedded in the knowledge bases, according to the judgment made by experts. Thus, our results seem compatible with our experts' view of what innovation risk at large pharmaceutical laboratories entails, and we provide all the necessary tools, files and datasets to replicate our results or to extend our fuzzy model.

From this perspective, we contribute to existing literature regarding innovation risk by capturing both success and failure when managing the drug pipeline. Our new 2-tuple method fuzzy methodological approach combines experts' knowledge from different fields with a variety of public datasets in a novel way. Therefore, our approach is novel in terms of the fuzzy method and in terms of the way we embed knowledge from different expert profiles and different datasets although it is based on previous contributions.

It should be highlighted that FIS have been proposed for decision making when managers are faced with complex and risky environments and the dataset is small but has many attributes (Li et al., 2011). In addition, risk issues are very relevant in deterring decision makers from expanding in the generic pharmaceutical business (Puente et al., 2011).

With the aim of determining whether a laboratory has a higher or lower innovation risk relative to other laboratories, we consider four input variables in two fuzzy subsystems (R&D expenditure, announced financial transactions, probabilities of success of authorized New Chemical Entities (NCEs) and probabilities of success of Clinical Trials (CTs)). The first fuzzy subsystem captures the financial side of innovation risk while the second one captures the pipeline side.

In our paper, innovation risk comparisons are made and graphical surfaces are analyzed in order to interpret the results. Correct application of this type of evaluation model requires that experts in the field devote enough time and effort to generating the knowledge base. Otherwise, the system would yield misleading results. We seek the evaluation of our model by sharing our graphical surfaces results with experts in the field who gave their insights about the feasibility and usefulness of our fuzzy model outcome and by running regressions where innovation risk is related to variables such as laboratory sales and debt. In section 4, our regressions suggest a negative and significant relationship between sales (or debt) and CFO innovation risk. Both sales and debt also capture the size effect. We also run additional regressions using a sales ratio and a debt ratio. We find a positive relationship between the sales ratio and CFO innovation risk, and a negative relationship between the debt ratio and CFO innovation risk. Also, CIO innovation risk is significant at the 10% level when the dependent variable is average debt. We perform additional robustness tests with lagged values of sales and debt (as instruments) in Appendix C.

The results of our evaluation model have been discussed with experts in order to evaluate the model and determine its usefulness for analyzing innovation risk, given the strategic choices of the 31 large pharmaceutical laboratories in our sample. It is also valid for carrying out a systematic analysis of innovation risk in other laboratories outside our sample. We provide all the necessary tools, files and data to replicate our results or to apply our new fuzzy model to a combination of different datasets.

Regarding possible extensions of our proposed methodology, small pharmaceutical laboratories are a relevant part of the pharmaceutical picture but are not covered in this paper (Schuhmacher et al. 2016; Macher and Boerner 2012) and advances in computational power are changing the way small labs may compete (Jamali et al. 2016). Wong et al. (2018) claim that previous estimates of drug development success rates, such as those by Thomas et al. (2016), rely on small databases that are not publicly available and may be subject to potential biases. In any case, it would be possible to re-estimate innovation risk at large pharma labs using the new estimates by Wong et al (2018).

When it comes to potential extensions related to the proposed fuzzy methodology, it would be possible to deepen in the establishment of consensus among experts in the relevant area. Thus, some restrictions

imposed in this work could be relaxed, allowing each expert to evaluate the model variables by proposing their own partitions independently of the rest of the evaluators (both in terms of the number of labels assigned to each variable and their parameterization) -see Herrera et al. (2000)-.

Other promising approaches for studying drug portfolio management and/or quantifying innovation risk may be based on simulation (Blau et al., 2004; Perez-Escobedo et al., 2011; Yu, 2012; Perez-Escobedo et al., 2012; Rosiello et al.. 2013), optimization (George and Farid 2008a; 2008b; Colvin and Maravelias, 2011; Laínez et al., 2012; Luo, 2012; Gibbert et al., 2014), real options (Bergemann and Hege, 1998; 2005; Ewens and Fons-Rosen, 2013; Ewens et al., 2014; Kerr and Nanda, 2015) and a combination of fuzzy and real options (Carlsson et al., 2007; Lo Nigro et al., 2016; Guo et al., 2018) or other related methodologies, sometimes mixing more than one methodology at a time. Irrespective of the actual methodology(ies) used, it is interesting to study the strategic choices faced by large pharmaceutical laboratories when trying to manage innovation risk and compete with both large and small laboratories. Finally, in this paper, we do not take into account time to approval, as in Macher and Boerner (2012) and Garzón-Vico et al. (2016), which may be an additional worth considering.

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Conflict of interest statement

The authors have no conflict of interest to declare.

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Appendix A. Data.

Table A.1. Sources of data for the construction of inputs.

Input (factor)	*Definition*	*Source*	*Comments*
R&D	Average expenditure per pharmaceutical laboratory in R&D from 2008 to 2013	Gascón et al. (2017). Table 12. Variable: I3-IRD	In Gascón et al. (2017) there are 37 laboratories in the sample. In our final sample there are 31. The following laboratories were removed from the initial sample: Celltrion, CSL, Hospira, Meda AB and Mitsubishi. Also, Merck KGAA and Merck & Co. data were merged because some CTs were not easy to classify between the two Mercks.
NFTs	Number of financial transactions per pharmaceutical laboratory from 2008 to 2013	Gascón et al. (2017). Table 6. Variable: Number of announced transactions	In Gascón et al. (2017) there are 37 laboratories in the sample. In our final sample there are 31. Table 6 contains information on the number of transactions (NFTs) and on the accumulated size of transactions. Both measures were considered although, in this paper, we only report the model with NFTs.
NCEs x Prob	Probabilities of success per ATC from Phase I to approval of New Chemical Entities authorized by EMA and FDA per pharmaceutical laboratory from 2008 to 2013	Authorized NCEs: Websites of the European Medicines Agency (EMA) and the Food and Drug Administration (FDA). Probabilities of success per ATC from Phase I to approval: Thomas et al. (2016)	Information on NCEs authorized by EMA and FDA per ATC code is combined with information on the probability of success per ATC from Phase I to Approval. Thomas et al. (2016) probabilities are specific to the biotech sector from 2006 to 2015 and we use these probabilities as a proxy for our sample of large pharmaceutical laboratories. Thus, we are assuming that all laboratories in our sample have the same probabilities of success when targeting a given disease covered by a given ATC code. Thomas et al. (2016) provide probabilities for 16 disease areas. With the aid of an expert in biochemistry, we converted these 16 disease areas into ATC codes in order to merge data from different sources (See Table A.2).
CTs x Prob	Probabilities of success per ATC from the corresponding phase (I, II, III and IV) of each CT to approval per pharmaceutical	CTs: Clinicaltrials.gov website Probabilities of success per ATC from the corresponding phase (I, II, III and IV) of the	Information on CTs per ATC code is combined with information on the probability of success per ATC from the corresponding pipeline phase of the CT to Approval. Information on CTs in Clinicaltrials.gov is classified, at the aggregate level, into 25 different conditions (disease areas). With the aid of an expert in biochemistry, we converted these 25 disease areas into ATC codes in order to merge data from different sources (See Table A.4 for details about expert associations that link CTs conditions to ATC codes).

	laboratory with starting date from 2008 to 2013	CT to approval: Thomas et al. (2016)	Moreover, CTs in Clinicaltrials.gov are reported at the sub-condition level (very detailed disease area). As of February 2017, there was a list that contained 6,232 sub-conditions (with some duplications because sometimes a given sub-condition belongs to more than one condition). For example, the sub-condition "Pain" belongs to two disease areas (Nervous system diseases and Symptoms and General Pathology) or the sub-condition "Digestive System Neoplasms" belongs to two disease areas (Cancers and Other Neoplasms and Digestive System Diseases). For our sample of 31 laboratories, we had to convert the sub-condition of each CT into a condition (disease area). Each CT may target more than one sub-condition and 99% of the CTs in our sample target six sub-conditions or less. We considered only the first six sub-conditions and we dropped the remaining sub-conditions of each CT (only 1% of the CTs targeted more than six sub-conditions). See Table A.7 for summary statistics and information on the exact matching procedure (exactly identified CTs with and without duplications). We ended up with two databases of CTs (one with perfectly identified sub-conditions with duplications, and another with no duplications). We combine condition (disease area converted into ATC codes) with Thomas et al. (2016) success probabilities from the corresponding phase to approval. See Table A.8 for summary statistics regarding CTs per phase. See Table A.5 for a description of the associations of clinicaltrial.gov conditions (disease areas) with ATC codes and to success probabilities in different pipeline phases from Thomas et al. (2016). Thomas et al. (2016) probabilities are specific to the biotech sector from 2006 to 2015. See previous comments in the NCEs x Prob factor.

Table A.2. Estimated probabilities of success of authorized NCEs from phase I to Approval.

ATC	*ATC Contents*	*Disease* *Thomas et al. (2016)*	*(i) Phase I to Approval* *Thomas et al. (2016)*	*(ii) Start equivalent*
A	Alimentary tract and metabolism	Metabolic	15.3%	6.54
B	Blood and blood forming organs	Hematology	26.1%	3.83
C	Cardiovascular system	Cardiovascular	6.6%	15.15
D	Dermatologicals	Other	16.3%	6.13
G	Genito-urinary system and sex hormones	Urology	11.4%	8.77
H	Systemic hormonal preparations, excluding sex hormones and insulins	Endocrine	13.2%	7.58
J	Antiinfectives for systemic use	Infectious disease	19.1%	5.24
L	Antineoplastic and immune-modulating agents	Oncology	5.1%	19.61
M	Musculo-skeletal system	Other	16.3%	6.13
N	Nervous system	Neurology	8.4%	11.90
P	Antiparasitic products, insecticides and repellents	Other	16.3%	6.13
R	Respiratory system	Respiratory	12.8%	7.81
S	Sensory organs	Ophthalmology	17.1%	5.85
V	Various	Other	16.3%	6.13

Note. This table combines information on 1) ATC codes and 2) Phase I to Approval probabilities of success from Thomas et al. (2016). With the aid of an expert in biochemistry, we converted disease areas from Thomas et al. (2016) into ATC codes. When a clear association between a given disease area and an ATC code did not exist, the probability associated with "other" diseases (16.30%) was used. Information on probabilities from phase I to approval may be interpreted using the start-equivalent approach. That is to say, for ATC code A, the probability in column (i) is 15.3% which implies in column (ii) that 6.54 new ATC-code A drugs are needed at the starting point (phase I) in order to obtain, on average, an authorized NCE in this ATC code.

Table A.3. Authorized NCEs per pharmaceutical laboratory and average probabilities of success of NCEs adjusting for ATC codes.

Lab Number	*Laboratory*	*(i) NCEs authorized per Lab*	*(ii) Sum of Probabilities*	*(iii) NCEs x Prob*
1	ABBOTT	1	0.066	6.60%
2	ALLERGAN	1	0.191	19.10%

3	AMGEN	5	1.011	20.22%
4	ASTELLAS	7	0.695	9.93%
5	ASTRAZENECA	10	1.663	16.63%
6	BAYER	10	1.366	13.66%
7	BIOGEN	2	0.168	8.40%
8	BRISTOL	8	1.14	14.25%
9	CELGENE	6	0.446	7.43%
10	EISAI	7	0.591	8.44%
11	ELI LILLY	5	0.883	17.66%
12	GILEAD	7	1.309	18.70%
13	GLAXOSMITHKLINE	27	3.345	12.39%
14	H.LUNDBECK	4	0.405	10.13%
15	IPSEN	1	0.163	16.30%
16	J&J	6	1.038	17.30%
17	MEDICINES COMPANY	1	0.066	6.60%
18	MERCK^2	16	2.205	13.78%
19	NOVARTIS	40	4.376	10.94%
20	NOVO NORDISK	6	1.134	18.90%
21	ORION	4	0.336	8.40%
22	OTSUKA	3	0.216	7.20%
23	PFIZER	15	1.46	9.73%
24	REGENERON	3	0.273	9.10%
25	RICHTER	1	0.114	11.40%
26	ROCHE	9	0.459	5.10%
27	SANOFI	18	2.38	13.22%
28	SHIRE	5	0.591	11.82%
29	TAKEDA	21	2.761	13.15%
30	TEVA	5	0.681	13.62%
31	UCB	4	0.27	6.75%
	TOTAL	258	31.802	12.33% *

Note. This table combines information on authorized NCEs at the ATC code level from our sample of 31 laboratories in the period 2008-2013 with information on success probabilities from Phase I to Approval from Thomas et al. (2016). Column (i) contains the number of authorized NCEs per lab. Column (ii) is the sum of probabilities, adjusting for the ATC code of each authorized NCE, per lab. Our input variable 3, NCEs x Prob, is calculated in Column (iii) which is equal to column (ii) divided by column (i). Thus, column (iii) contains the average probability of success per laboratory based on authorized NCEs adjusting for ATC code. On average the laboratories in our sample have a 12.33% probability of success (FDA or EMA approval) when they start researching at Phase I, based on authorized NCEs. See also Table I for a more detailed description of the calculation of the NCEs x Prob variable in column (iii).

Table A.4. Association of Clinicaltrials.gov conditions (disease areas) to ATC codes.

ATC	*Condition number (disease area number)*	*Condition description (disease description)*
J	1	Bacterial and Fungal Diseases
N	2	Behaviors and Mental Disorders
B	3	Blood and Lymph Conditions
L	4	Cancers and Other Neoplasms
A	5	Digestive System Diseases
V	6	Diseases and Abnormalities at or before Birth
V	7	Disorders of Environmental Origin
S	8	Ear, Nose, and Throat Diseases
S	9	Eye Diseases
H	10	Gland and Hormone Related Diseases
C	11	Heart and Blood Diseases
L	12	Immune System Diseases
V	13	Mouth and Tooth Diseases
M	14	Muscle, Bone, and Cartilage Diseases
N	15	Nervous System Diseases
A	16	Nutritional and Metabolic Diseases
V	17	Occupational Diseases
P	18	Parasitic Diseases
R	19	Respiratory Tract (Lung and Bronchial) Diseases
D	20	Skin and Connective Tissue Diseases
V	21	Substance Related Disorders
V	22	Symptoms and General Pathology
G	23	Urinary Tract, Sexual Organs, and Pregnancy Conditions
J	24	Viral Diseases
V	25	Wounds and Injuries

Note. This table combines information on 1) ATC Codes and 2) CTs conditions (25 disease areas) from Clinicaltrials.gov. With the aid of an expert in biochemistry, we converted CTs disease areas (conditions) from Clinicaltrials.gov into ATC codes. When a clear association between a disease area and an ATC code did not exist, the ATC V (various) was associated with the corresponding CTs disease area (condition).

Table A.5. Association of Clinicaltrials.gov conditions (disease areas) to ATC codes and to phase I to phase IV probabilities.

Condition number (Disease area)	*ATC*	*Disease Thomas et al. (2016)*	*Phase I to Approval*	*Phase II to Approval*	*Phase III to Approval*	*NDA/BLA to Approval*

1	J	Infectious disease	19.10%	27.50%	64.50%	88.70%
2	N	Neurology	8.40%	14.20%	47.80%	83.20%
3	B	Hematology	26.10%	35.70%	63.00%	84.00%
4	L	Oncology	5.10%	8.10%	33.00%	82.40%
5	A	Metabolic	15.30%	25.10%	55.50%	77.80%
6	V	Other	16.30%	24.40%	61.50%	88.40%
7	V	Other	16.30%	24.40%	61.50%	88.40%
8	S	Ophthalmology	17.10%	20.20%	45.20%	77.50%
9	S	Ophthalmology	17.10%	20.20%	45.20%	77.50%
10	H	Endocrine	13.20%	22.40%	55.90%	86.00%
11	C	Cardiovascular	6.60%	11.30%	46.70%	84.20%
12	L	Oncology	5.10%	8.10%	33.00%	82.40%
13	V	Other	16.30%	24.40%	61.50%	88.40%
14	M	Other	16.30%	24.40%	61.50%	88.40%
15	N	Neurology	8.40%	14.20%	47.80%	83.20%
16	A	Metabolic	15.30%	25.10%	55.50%	77.80%
17	V	Other	16.30%	24.40%	61.50%	88.40%
18	P	Other	16.30%	24.40%	61.50%	88.40%
19	R	Respiratory	12.80%	19.60%	67.30%	94.60%
20	D	Other	16.30%	24.40%	61.50%	88.40%
21	V	Other	16.30%	24.40%	61.50%	88.40%
22	V	Other	16.30%	24.40%	61.50%	88.40%
23	G	Urology	11.40%	20.00%	61.20%	85.70%
24	J	Infectious disease	19.10%	27.50%	64.50%	88.70%
25	V	Other	16.30%	24.40%	61.50%	88.40%

Note. This table combines information on 1) ATC Codes, 2) Clinicaltrials.gov conditions (25 disease areas) and 3) Probabilities of success from the corresponding phase of the CT to approval, from Thomas et al. (2016). These are the probabilities that we use when assessing the probability of success of a CT in a given pipeline phase. With the aid of an expert in biochemistry, we converted both CTs disease areas (conditions) from Clinicaltrials.gov and diseases from Thomas et al. (2016) into ATC codes. When a clear association did not exist, the ATC V (various) and/or the "other" disease was associated with the corresponding CTs disease area (condition) and probability. We interpret the probability of success from NDA/BLA to Approval as the probability of success from Phase IV to approval. New Drug Application (NDA) and Biologic License Application (BLA) probabilities.

Table A.6. CTs per pharmaceutical laboratory and average probabilities of success of NCEs adjusting for ATC codes and pipeline phase (with and without duplications).

Lab Number	*Laboratory*	*(i) Sum of Probabilities*	*(ii) Number of CTs*	*No duplications (iii) CTs x Prob*	*(iv) Sum of Probabilities*	*(v) Number of CTs*	*Duplications (vi) CTs x Prob*
1	ABBOTT	57.72	127	45.45%	91.10	210	43.38%
2	ALLERGAN	70.14	129	54.37%	96.69	182	53.13%
3	AMGEM	30.76	93	33.08%	38.87	131	29.67%
4	ASTELLAS	53.84	108	49.85%	83.75	167	50.15%
5	ASTRAZENECA	71.18	191	37.27%	100.65	290	34.71%
6	BAYER	83.40	220	37.91%	129.06	337	38.30%
7	BIOGEN	13.46	36	37.40%	25.95	71	36.54%
8	BRISTOL	133.04	355	37.48%	222.01	585	37.95%
9	CELGENE	31.61	158	20.00%	78.04	414	18.85%
10	EISAI	16.17	41	39.44%	21.45	57	37.63%
11	ELI LILLY	104.81	279	37.57%	178.04	484	36.79%
12	GILEAD	49.54	121	40.95%	92.77	231	40.16%
13	GLAXOSMITHKLINE	270.38	790	34.23%	404.16	1220	33.13%
14	H. LUNDBECK	10.90	27	40.37%	12.70	30	42.35%
15	IPSEN	5.72	14	40.84%	11.22	29	38.71%
16	J&J	136.36	267	51.07%	228.90	486	47.10%
17	MEDICINES COMPANY	217.53	549	39.62%	330.48	878	37.64%
18	MERCK^2	206.82	510	40.55%	317.01	816	38.85%
19	NOVARTIS	189.42	482	39.30%	305.30	794	38.45%

20	NOVONORDISK	79.99	201	39.79%	165.75	432	38.37%
21	ORION	10.98	27	40.66%	17.08	49	34.85%
22	OTSUKA	35.27	86	41.01%	46.38	126	36.81%
23	PFIZER	207.87	566	36.73%	330.45	925	35.72%
24	REGENERON	18.16	53	34.27%	25.70	75	34.26%
25	RICHTER	4.28	10	42.79%	4.68	13	35.97%
26	ROCHE	91.84	214	42.92%	159.33	387	41.17%
27	SANOFI	175.97	364	48.34%	269.75	558	48.34%
28	SHIRE	21.20	47	45.10%	38.06	88	43.25%
29	TAKEDA	43.70	92	47.50%	64.58	131	49.30%
30	TEVA	19.59	54	36.27%	38.44	107	35.92%
31	UCB	24.85	76	32.70%	34.07	111	30.69%
	Total	2486.5	6287	39.55%	3962.4	10414	38.05%

Note. This table combines information on CTs at the ATC code level from our sample of 31 laboratories in the period 2008-2013 with information on success probabilities from the corresponding phase (I to IV) to Approval from Thomas et al. (2016), with and without duplications in the CTs (see comments in Table A.1 regarding CTs). Column (i) contains the sum of probabilities from the corresponding phase to approval (adjusting for ATC code). Column (ii) is the number of CTs per lab. Our input variable 4 is CTs x Prob which is calculated (with no CT duplications) in Column (iii), which is equal to column (i) divided by column (ii). Thus, column (iii) contains the average probability of success per laboratory based on CTs adjusting for phase and for ATC code. On average the laboratories in our sample have a 39.55% probability of success in their average CT and their average phase. See also Table A.1 for a more detailed description of calculation of the CTs x Prob variable in column (iii). In the case of CT duplications, our input variable 4 is again CTs x Prob although it is calculated in Column (vi). For more information regarding the calculation of probabilities with and without duplications, see also Table A.7.

Table A.7. Exactly identified CTs per step (COND1 to COND 6).

COND	*(i) Exactly identified CTs (without duplications)*	*(ii) Exactly identified CTs (with duplications)*
COND1	5487	9025
COND2	664	1168
COND3	88	138
COND4	24	41
COND5	15	24
COND6	9	18
Total	6287	10414

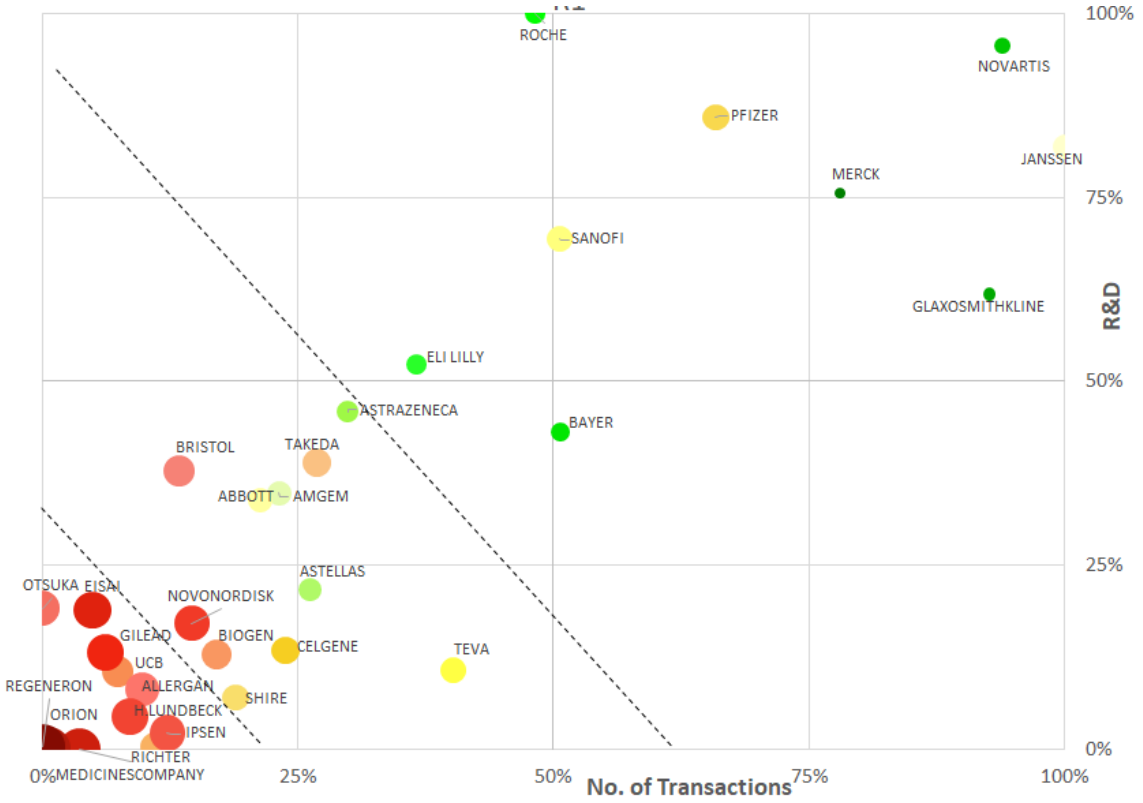
Note. In order to identify the condition (disease area) of each CT in our final sample, we imposed an exact match between the sub-condition of the CT and a sub-condition from the list of 6,232 sub-conditions. In an iterative way, in a first step, we searched for an exact match in the first sub-condition of each CT (COND1). A total of 5,487 CTs, with no duplications, column (i), were identified. We added these 5,487 CTs with an exact match in COND1 to our final sample of CTs. With the remaining CTs with no perfect match, in a second step, we searched for an exact match in the second sub-condition of each remaining CT (COND2) for the CTs targeting two sub-conditions or more. We also added these 664 CTs with an exact match in COND2 and no duplications to our final sample of CTs. With the remaining CTs, we followed a similar procedure for COND3, COND4, COND5 and COND6 (until we reached our sixth and last sub-condition). Our final sample of CTs has 6,287 CTs with no duplications. After completing these recurrent six steps, we had perfectly identified the condition of a total of 6,287 clinical trials, with no duplications, in our sample of 31 large pharmaceutical laboratories (see Table A.6) and, following a similar procedure, in column (ii), a total of 10,414 CTs, with duplications, in the same sample. See also comments in Table A.1 on CTs data.

Table A.8. Exactly identified CTs per pipeline phase.

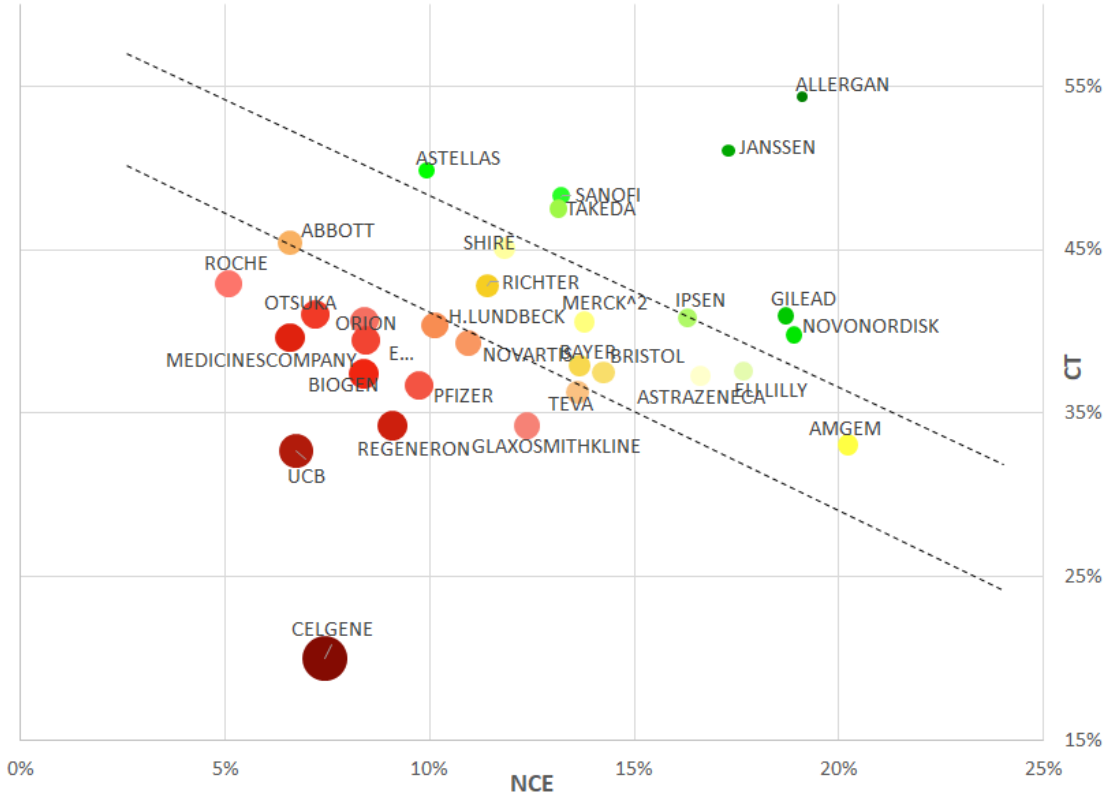
Pipeline Phases	*CTs per phase (without duplications)*	*CTs per phase (with duplications)*
Early Phase 1	12	22
Phase 1	1373	2319
Phase 1|Phase 2	186	379
Phase 2	1629	2827
Phase 2|Phase 3	93	145
Phase 3	1907	3078
Phase 4	1087	1644
Total	6287	10414

Note. This table contains summary information regarding the distribution in our sample of CTs among pipeline phases. We use more detailed information from Thomas et al. (2016) in order to obtain the probabilities from the corresponding pipeline phase to approval at the ATC code level. See also comments in Table A.1. In the case of calculation of the probability from Early Phase 1 to approval in a given ATC, we decided to apply half the probability from phase I to approval. In the case of calculation of the probability from Phase 1|Phase 2 to approval in a given ATC, we decided to apply an average of the corresponding probabilities (from phase 1 to approval and from phase 2 to approval). In the case of calculation of the probability from Phase 2|Phase 3 to approval in a given ATC, we decided to apply an average of the corresponding probabilities (from phase 2 to approval and from phase 3 to approval).

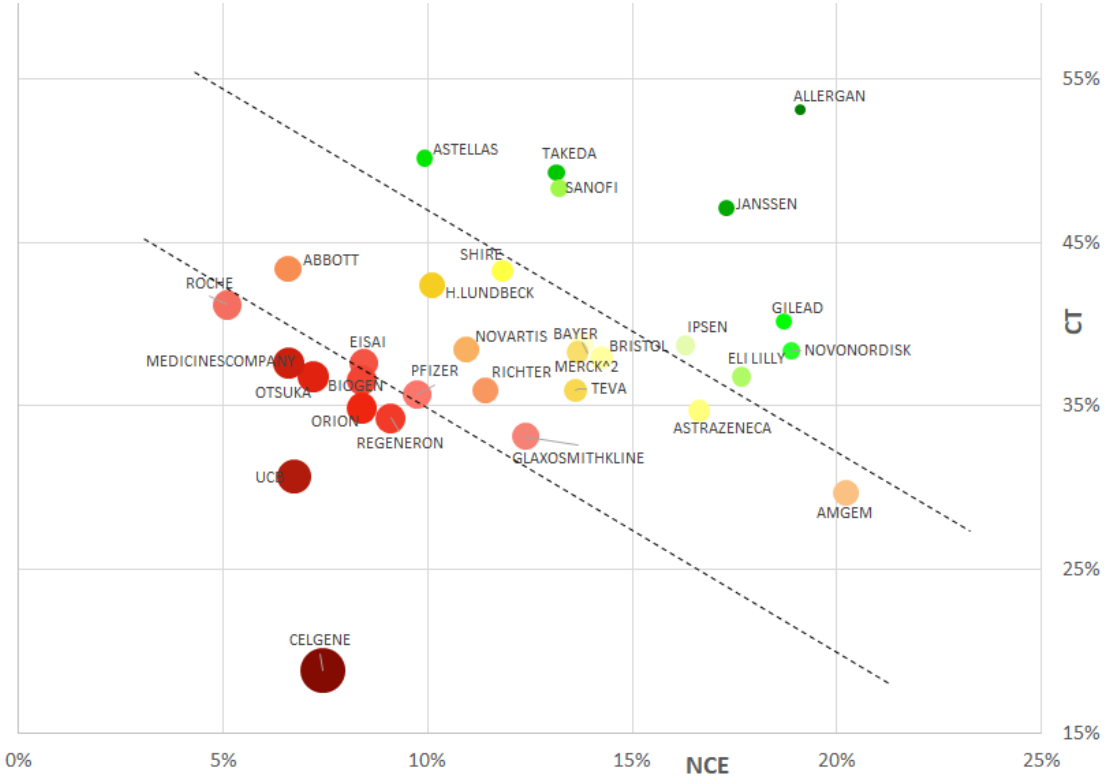
Appendix B. Risks R1 and R2 of the pharmaceutical laboratories.



a) Risk R1



b) Risk R2, without duplications



c) Risk R2, with duplications

Figure B.1. Risks R1 and R2 of the 31 pharmaceutical laboratories analyzed.

Appendix C. OLS Robustness tests. Use of instruments in regressions.

In order to run additional robustness tests, we chose innovation risk as the dependent variable[4], given that we are in a position to use instruments when the independent variables are total assets, market capitalization, debt or sales. First, we included, as an independent variable, average total assets in the period 2008 to 2013 and in the period 2002 to 2007. The reason for calculating the average from 2002 to 2007 is to use a lagged variable that may be a valid instrument in the case of endogeneity problems. With this instrument, we try to avoid endogeneity and causality problems in the estimates in the period 2002 to 2007 although we also present results with independent variables in the period 2008 to 2013 (see section 4).

See correlation matrix of instruments in Table C.1.

Table C.1. Correlation matrix of instruments (period 2002 to 2007).

	Avg Sales	Sales Rat.	Avg Debt	Debt Rat.	Avg Ta.	Avg MCap
Avg Sales	1.0000	-	-	-	-	-
Sales Rat.	0.1662	1.0000	-	-	-	-
Avg Debt	0.8591	0.0263	1.0000	-	-	-
Debt Rat.	0.1543	-0.1757	0.4182	1.0000	-	-
Avg Ta.	0.9134	-0.0790	0.8598	0.0868	1.0000	-
Avg MCap	0.8790	0.0703	0.6729	0.0548	0.8558	1.0000

Note. The average of each variable is calculated in the period 2002 to 2007 in order to try to avoid possible spurious correlations between measures of innovation risk (calculated in the period 2008 to 2013) and explanatory variables (calculated in the period 2002 to 2007). Avg Sales are average sales of each pharmaceutical laboratory in the period 2002 to 2007. Sales Rat. is the ratio of sales to total assets in the same period. Avg Debt is average debt while Debt Rat. is the ratio of debt to total assets. Avg Ta. is average total assets and Avg Mcap is average market capitalization in the period 2002 to 2007.

Table C.2 contains four regressions where the dependent variable is one of the four measures of innovation risk calculated in the period 2008 to 2013 and, as instruments, we use two independent variables (average sales in the period 2002 to 2007 and average debt in the period 2002 to 2007). With these (lagged values of variables sales and debt) instruments we try to avoid capturing spurious

[4] In section 4, we run OLS regressions where, for example, sales is the dependent variable and a measure of innovation risk is the independent variable. With this approach, we obtain a negative and significant relationship between sales and innovation risk. However, when using the same time period (2008 to 2013) for calculating innovation risk and average sales in the period, there are concerns regarding causality and, also, endogeneity issues may arise. In order to deal with these concerns, we run OLS regressions where the independent variable is average sales in the period 2002 to 2007 (in order to compare results, we also run the regression with contemporaneous sales in the period 2008 to 2013, which is the period that we use in the fuzzy model to obtain innovation risk results).

relationships between innovation risk in the period 2008 to 2013 and sales (or debt) in the period 2008 to 2013. R-squared of the regressions with instruments are in the range of 41%-42% for CFO innovation risk and of 10%-12% for CIO innovation risk.

Table C.2. Summary of the results of the regression models with lagged independent variables.

	CFO (i) CT dup	CFO (ii) CT no dup	CIO (iii) CT dup	CIO (iv) CT no dup
Avg Sales	-5.64e-09	-6.08e-09*	-5.00e-09	-5.52e-09**
	(3.73e-09)	(3.31e-09)	(2.71e-09)	(2.44e-09)
Avg Debt	1.12e-12	1.30e-09	1.16e-08*	1.30e-08*
	(1.03e-08)	(8.84e-09)	(7.51e-09)	(7.01e-09)
Constant	0.738***	0.735***	0.635***	0.622***
	(0.024)	(0.026)	(0.039)	(0.037)
R-squared	0.414	0.422	0.102	0.125
No. observations	29	29	29	29

Note: The dependent variable in each regression is a measure of innovation risk calculated in the period 2008 to 2013: (i) CFO with CT duplications, (ii) CFO without CT duplications, (iii) CIO with CT duplications and (iv) CIO without CT duplications. The explanatory variables are average sales in the period 2002 to 2007 and average debt in the period 2002 to 2007. In addition, *, **, *** indicate significance at the 1, 5 and 10% levels. Bootstrap Standard errors in parentheses.

We also use ratios as instruments (sales to total assets ratio and debt to total assets ratio in the period 2002 to 2007) but relationships are not significant at the 10% level.

As an additional instrument for size, we considered average total assets in the period 2002 to 2007, which is significant at the 5% level when the dependent variable is CFO innovation risk but not significant at the 10% level when the dependent variable is CIO innovation risk. An alternative way to approximate size is market capitalization, in which case we find similar results.

Furthermore, we also run several OLS regressions with bootstrapping (without trying to infer causality) of risk on efficiency (the three efficiency measures in Gascón et al (2017)). In the regressions we mostly find a negative relationship between risk and efficiency although it is not always significant at the ten percent level.

Appendix D. Numerical results.

Table D.1. Global innovation risk. CFO versus CIO perspective.

	Chief Financial Officer (CFO) OUTPUT31 Global innovation risk CTs without duplications	Chief Innovation Officer (CIO) OUTPUT32 Global innovation risk CTs without duplications	Chief Financial Officer (CFO) OUTPUT31 Global innovation risk CTs with duplications	Chief Innovation Officer (CIO) OUTPUT32 Global innovation risk CTs with duplications
ABBOTT	68.1%	68.1%	68.2%	70.6%
ALLERGAN	62.0%	31.9%	62.0%	31.9%
AMGEM	62.0%	57.0%	66.1%	68.8%
ASTELLAS	56.8%	49.5%	56.3%	48.6%
ASTRAZENECA	57.1%	54.5%	58.6%	58.0%
BAYER	52.1%	55.8%	52.0%	55.5%
BIOGEN	74.4%	73.9%	74.4%	74.2%
BRISTOL	71.3%	57.9%	71.0%	57.4%
CELGENE	72.1%	88.9%	72.1%	88.9%
EISAI	85.0%	72.9%	84.7%	73.6%
ELI LILLY	53.4%	51.7%	53.7%	52.3%
GILEAD	71.0%	48.5%	71.3%	49.0%
GLAXOSMITHKLINE	39.0%	55.2%	39.1%	57.2%
H. LUNDBECK	82.2%	70.9%	82.2%	70.3%
IPSEN	72.2%	52.9%	73.1%	54.6%
JANSSEN	52.8%	39.6%	56.4%	46.3%

MEDICINES COMPANY	88.4%	74.2%	88.0%	75.7%
MERCK^2	32.4%	45.0%	32.6%	45.8%
NOVARTIS	47.8%	58.9%	47.8%	59.2%
NOVONORDISK	70.2%	48.7%	70.7%	49.7%
ORION	88.8%	72.4%	88.2%	75.0%
OTSUKA	80.9%	73.2%	80.5%	75.5%
PFIZER	71.6%	72.6%	71.6%	73.0%
REGENERON	88.3%	74.5%	88.3%	74.5%
RICHTER	71.0%	61.8%	74.4%	70.7%
ROCHE	54.0%	64.2%	54.0%	65.6%
SANOFI	60.4%	49.8%	60.4%	49.8%
SHIRE	65.4%	56.9%	66.6%	59.1%
TAKEDA	63.4%	51.1%	61.9%	48.3%
TEVA	67.3%	62.3%	67.5%	62.9%
UCB	76.2%	78.5%	76.0%	79.6%

Note. The third fuzzy model combines the two previous fuzzy subsystems in order to evaluate global innovation risk in large pharmaceutical laboratories. The first subsystem mainly captures the financial side of innovation risk while the second approximates the pipeline side. Based on the risk values obtained in the two previous subsystems, the third subsystem captures the overall innovation risk associated with each laboratory. In this third subsystem, we allow for two different perspectives, those of the Chief Financial Officer (CFO) and the Chief Innovation Officer (CIO). Results are presented taking into account CTs with and without duplications (see comments in Table A.1 regarding CTs).